Brief Outline

1. **Colorado** (used through August 2014)
2. **Colorado** (used starting August 2014)
3. **Finland** – only used in Tampere at very beginning of study (never used in Oulu or Turku); *Finland informs by phone and at next visit; does not send a letter*
4. **Germany**
5. **Georgia/Florida** (used through August 2013)
6. **Georgia/Florida** (used August 2013 – September 2014)
7. **Georgia/Florida** (used starting September 2014)
8. **Washington**
9. *Sweden informs at next visit; does not send a letter*

F. Model Letter for Reporting First-Time Multiple Positive Antibody Results (child's results)

G. Site Specific Letter for Reporting First-Time Multiple Positive Antibody Results (child's results)

1. **Washington**
2. **Colorado** (used starting August 2014)

H. Model Telephone Script for Reporting Single Persistent Positive Antibody Results

I. Model Letter for Reporting Single Persistent Positive Antibody Results

J. Site Specific Letter for Reporting Single Persistent Positive Antibody Results

1. **Colorado** (used starting August 2014)
2. **Germany** (used starting August 2014)
3. **Georgia** (used starting September 2014)
4. **Washington** (used August 2014 – July 2017)
5. **Washington** (used starting July 2017)

K. Site Specific Letter for Reporting ≥ Second-time Positive Antibody Results (for child's results)

1. **Colorado**
2. **Germany**
3. **Georgia/Florida** (used through August 2013)
4. **Georgia/Florida** (used starting in August 2013)
5. **Washington**
6. **Sweden** (used starting in September 2014)
7. *Sweden informs at next visit; does not send a letter (up until September 2014)*
8. *Finland informs by phone and at next visit; does not send a letter*

1. **Finland** (used starting September 2017)

BB. Model Unable to Test for All Antibodies due to Insufficient Volume Letter (child's results)

1. **Colorado**

CC. Model Maternal Blood Draw Informed Consent Form (for AB testing)

DD. Model Telephone Script for Reporting Maternal Antibody Negative Results

EE. Model Telephone Script for Reporting Maternal Antibody Positive Results (same marker as infant)

FF. Model Telephone Script for Reporting Maternal Antibody Positive Results (different marker than infant)

GG. Model Phone Script For Reporting Positive Celiac Disease Antibody Results

HH. Model Celiac Disease Information Sheet

II. Model Letter for Reporting Positive Celiac Disease Test Results

JJ. Site Specific Letter for Reporting Positive Celiac Disease Antibody Results

1. **Colorado**
2. **Germany**
3. **Georgia**
4. **Florida**
5. **Washington**
6. *Sweden informs at next visit; does not send a letter*
7. *Finland informs by phone and at next visit; does not send a letter*

KK. Model Letter for Reporting Positive Celiac Disease Antibody Results to Pediatric Gastroenterologist

LL. Site Specific Letter for Reporting Negative Celiac Disease Antibody Result after a Positive Celiac Disease Antibody

1. **Colorado**
2. *Sweden informs at next visit; does not send a letter*
3. *Finland informs by phone and at next visit; does not send a letter*

MM. Site Specific Letter for Reporting Negative Celiac Disease Antibody Results

1. **Colorado**
2. **Georgia/Florida**
3. **Washington**

This Manual of Operations (MOO) has been created to provide details concerning the design, conduct, performance, monitoring, recording, analysis, and reporting of the TEDDY study to assure that the data and reporting results are accurate and that the rights, integrity, and confidentiality of the subjects are protected.

1. Summary and Objectives

1.1. Summary

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Disease (NIAID), National Institute of Child Health and Human Development (NICHD), National Institute of Environmental Health Sciences (NIEHS), Juvenile Diabetes Research Foundation (JDRF), and Centers for Disease Control and Prevention (CDC) have established a consortium of six Clinical Centers (CC) and a Data Coordinating Center (DCC) to develop and carry out studies to identify environmental causes of T1DM in genetically susceptible individuals.

The Environmental Determinants of Diabetes in the Young (TEDDY) study will investigate genetic and genetic-environmental interactions, including gestational infection or other gestational events, childhood infections or other environmental factors after birth, in relation to the development of prediabetic autoimmunity and Type I Diabetes Mellitus (T1DM). The consortium of six centers has been assembled to participate in the development and implementation of studies to identify environmental factors that trigger the development of T1DM in genetically susceptible individuals.

Epidemiologic patterns suggest that viruses, nutrition, toxic agents or socioeconomic psychosocial factors may contribute to the etiology alone or in combination. Elucidation is confounded by the long interval between exposure and onset of clinical disease, as well as the interaction of multiple genes and/or insults, which appear to interact in a complex manner. Numerous studies have investigated environmental influences but have yielded conflicting results. This may be in part due to the failure to account for genetic susceptibility, begin observation at early ages or *in utero*, and/or monitor subjects long term and frequently.

The CCs will recruit and enroll subjects, including obtaining informed consent from parents prior to or shortly after birth, obtain genetic and other samples from neonates and parents, and prospectively follow selected neonates throughout childhood or until development of islet autoimmunity or T1DM.

The TEDDY Consortium will allow for a coordinated, multi-disciplinary approach to this complex disease. Collection of information and samples in a standardized manner will achieve greater statistical power than smaller independent investigations. The TEDDY study will establish a central repository of data and biologic samples for subsequent hypothesis based research.

Data will be gathered from cohorts of newborns from the general population and newborn first-degree relatives of probands with T1DM. Newborns will first be identified to be at genetic risk for T1DM before long term follow-up. These cohorts are to be followed for 15 years for the appearance of various beta-cell autoantibodies and diabetes, with documentation of early childhood diet, reported and measured infections, vaccinations, and psychosocial stressors.

The TEDDY study proposes to newly recruit 7,013 neonates from the general population with a pre-determined type 1 diabetes risk of 3% and 788 neonates with first degree relatives who have type 1 diabetes and who have a pre-determined type 1 diabetes risk of 10%. Thus, we propose to study a total of 7,801 participants across six clinical centers worldwide (Finland, Germany, Sweden and three in North America). The North American Centers are expected to recruit 40% of the 7,801 participants. The participants will be followed with blood sampling every three months for islet autoantibody measurements until age 4 years and then every six months until the age of 15, for a projected total of approximately 100,000 samples over the first 5 years of the study, and a projected total of approximately 250,000 over the entire study.

Results from previous studies have been confounded by imprecise assessment of exposure, recall bias, failure to account for genetic susceptibility, failure to assess exposures at very early ages or the inability to follow a sufficient sample of children long-term with high intensity. The present multi-center study will provide an opportunity to fill important gaps in our understanding of the events leading to T1DM by studying from birth high-risk general population children and relatives and by systematic screening of candidate environmental and genetic factors. We will apply "cutting edge" molecular immunologic and genetic techniques to samples collected in six cohorts of high-risk children. In addition, samples collected by TEDDY will create a valuable resource for investigators proposing innovative hypotheses concerning candidate environmental and genetic factors.

The long-term goal of the TEDDY study is the identification of infectious agents, dietary factors, or other environmental agents, including psychosocial factors which trigger T1DM in genetically susceptible individuals or which protect against the disease. Identification of such factors will lead to a better understanding of disease pathogenesis and result in new strategies to prevent, delay or reverse T1DM.

1.2. Objectives

The primary objective of this study is to identify environmental factors that predispose to or protect from beta-cell autoimmunity and T1DM.

The secondary objectives include:

1. Identification of potential differences in the environmental determinants of T1DM across diverse populations and ethnic groups.
2. Identification of potential differences in the environmental determinants of T1DM between children with and without first-degree T1DM relatives.

3. Establishment of a central repository for data and biologic samples for subsequent hypothesis based research.
4. Exploration of psychosocial corollaries of the ascertainment of risk status for autoimmunity and T1DM in newborns.
5. Exploration of gene-environmental interactions.
6. Better understanding of the natural history of the disease.

1.3. Hypothesis

1. Initiation of persistent beta-cell autoimmunity and progression from beta-cell autoimmunity to diabetes is increased with:
   a. Exposure to a trigger factor during pregnancy, such as infections, preeclampsia, blood incompatibility, or birth weight.
   b. Differences in the timing of the introduction and/or the type of dietary constituents that include exposure to cereals or gluten, exposure to cow's milk during infancy and/or childhood, and short duration of breast-feeding;
   c. Lower intake of serum 25 hydroxyvitamin D in early infancy, vitamin E, anti-oxidants (e.g., carotenoids, ascorbic acid, selenium, or omega-3 fatty acids);
   d. Higher frequency of specific (e.g., enterovirus, rotavirus, or bacterial) infections, or non-specific childhood infections including those that exhibit molecular mimicry;
   e. Increased exposure to routine childhood immunizations and their timing;
   f. Environmental factors that may be contained in drinking water (e.g., low concentrations of zinc or high concentrations of nitrates, or lower pH levels);
   g. Exposure to household pets, and various allergies;
   h. Excessive weight gain;
   i. Increased psychological stress.

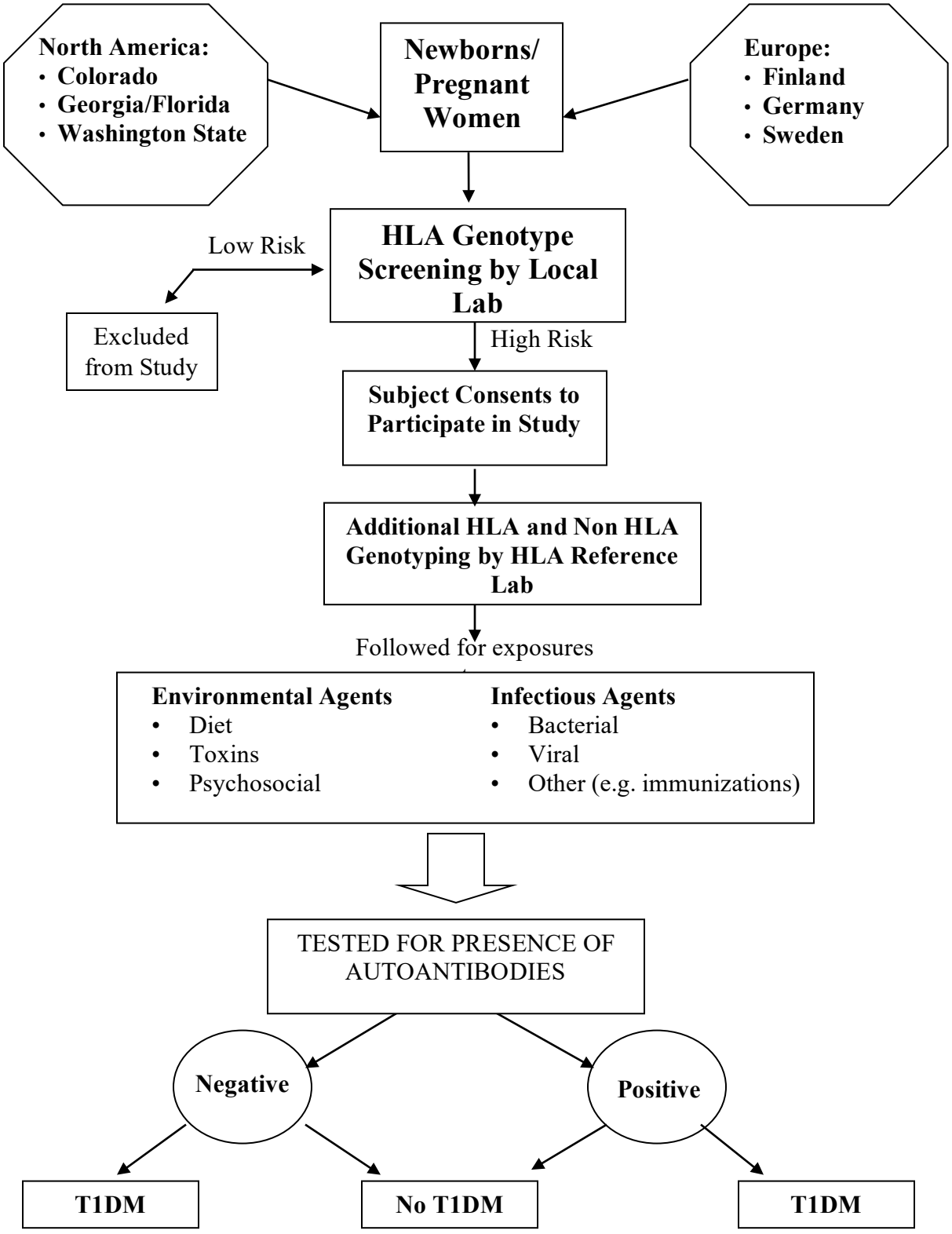
2. The risk of persistent beta-cell autoimmunity is lower in children from the general population than in offspring or siblings of T1DM patients when stratifying for the HLA DR-DQ genotype and exposure to environmental triggers.

3. The interaction of HLA DR-DQ genotype with exposure to dietary or infectious factors leads to increased incidence of beta-cell autoimmunity and T1DM.

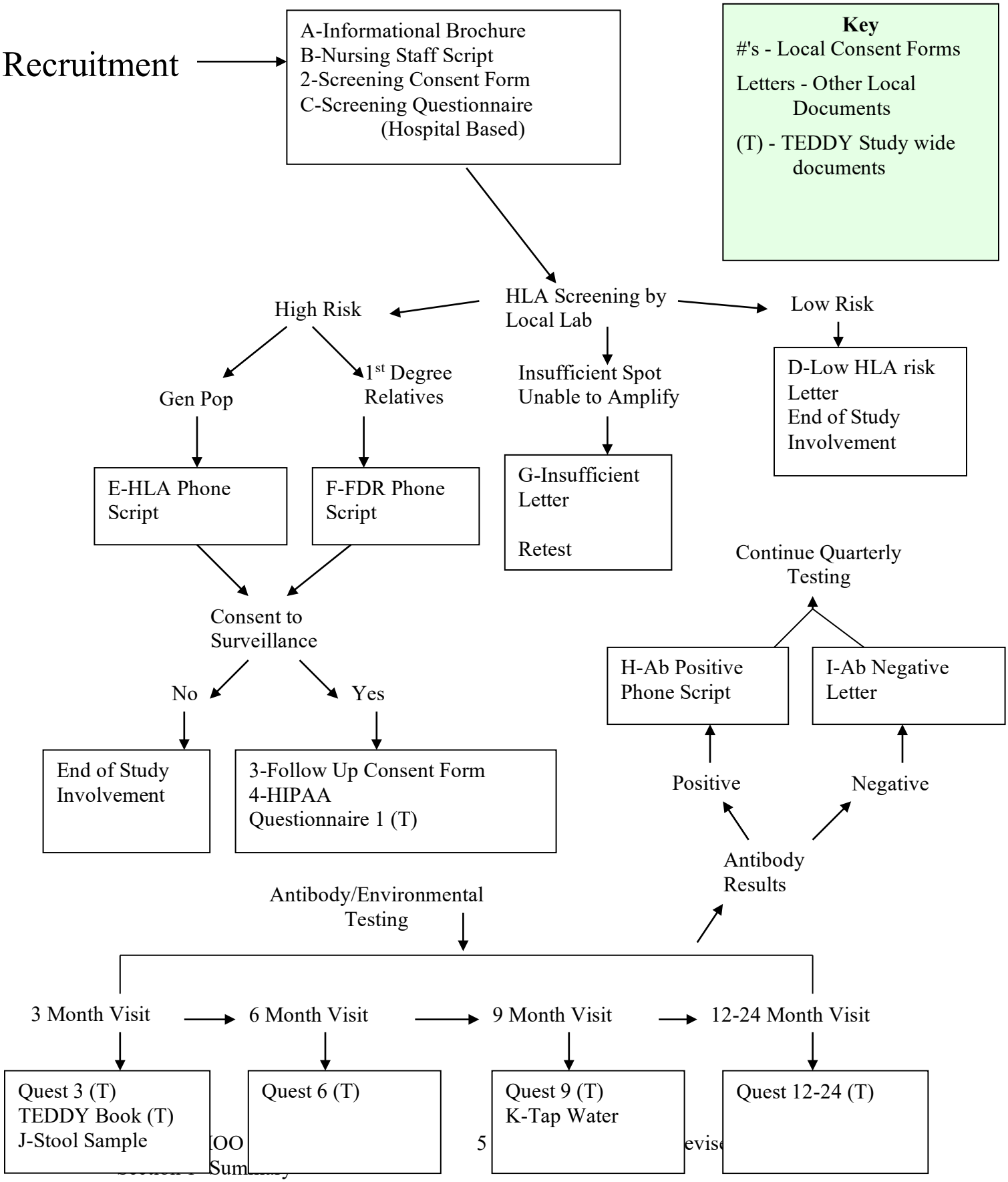
4. We expect that in some families study participation will be associated with affective (anxiety, depression) and behavioral responses (e.g. actions to prevent possible T1DM).

1.4 Overview Flow Charts

1.4.1 Study Design



1.4.2 Flow of Study Documents (attached proposal, based on Seattle)



2. Study Organization

2.1. Committees

2.1.1. Steering Committee

Function of the Steering Committee: The Steering Committee has overall responsibility for the design, planning, execution, and publication of the research performed by the TEDDY Study Group. The Steering Committee will approve all protocols, changes to protocols, and manuals of operations.

Examples of Steering Committee functions include (but are not limited to):

- Responsibility for approval and final development of Study Protocols
- Responsibility for implementation of studies at the various Clinical Centers
- Maintenance of surveillance of TEDDY study performance
- Development of the Policies of TEDDY itself, and formulation and development of policies for the various committees, centers, and reference laboratories
- Receiving and acting upon reports and recommendations of various committees
- Reviewing matters relevant to the administrative, financial, medical, legal, and ethical considerations, or functions of TEDDY

Voting Members of the Steering Committee:

- Director of the Data Coordinating Center (1)
- PI's from each of the Clinical Centers (6)
- Representative of the funding institutes of NIH (1)

Rules of the Steering Committee:

- The Steering Committee meets in person at least annually.
- Additional meetings of the Steering Committee may be called by the Chairs of the Steering Committee or by a majority of the members of the Steering Committee.
- These additional Steering Committee meetings may be in person or by other means.
- Notice of all Steering Committee meetings must be given at least two weeks in advance of such meetings.
- Fifty percent (50%) of the voting membership of the Steering Committee constitutes a quorum. Seventy-five percent (75%) of the voting membership of the Steering Committee constitutes a quorum for consideration of changes to the approved TEDDY Protocol.
- Any action items may be approved by majority vote of the Steering Committee. A supermajority of 75% of the full committee is required for adoption of changes to the approved TEDDY Protocol.

- Adoption of changes to the approved TEDDY Protocol must be reviewed by the External Evaluation Committee (EEC) and by NIH.

The Chairs of Steering Committee:

- The Chairs serve at the pleasure of the NIH for an undesignated term.
- It is the intent of the NIH that the Chairs of the Steering Committee have substantial authority to act for the Steering Committee to further the goals of TEDDY.
- The Chairs may create Working Committees as needed, and shall appoint the members and chairs of these Working Committees.
- The Chairs appoint committee chairpersons and may rotate these positions annually. All committee chairs serve for undesignated terms.

2.1.2 Executive Committee

Function of the Executive Committee: The Executive Committee coordinates the fiscal aspects of TEDDY grant and advises the Steering Committee of its actions.

Membership of the Executive Committee:

- The Chairs of the Steering Committee (2)
- Representative of NIDDK (1)

2.1.3 Ancillary Studies Committee

Function of the Ancillary Studies Committee:

- Review proposed ancillary studies and make recommendations according to approved TEDDY policy.
- Recommend changes to policy as necessary and in light of proposed ancillary studies.
- Provide recommendations to the Steering Committee with regard to the use of retained screening samples for subjects not eligible for TEDDY study protocol.

See Appendix for the TEDDY Ancillary Studies Policy.

2.1.4 Celiac Disease Committee

Function of the Celiac Disease Committee:

- Create data capture forms and elements for children with suspected and confirmed Celiac Disease

2.1.5 Clinical Implementation Committee

Function of the Clinical Implementation Committee:

- Monitor and answer questions related to medication and ICD-10 coding
- Monitor and answer questions related to Adverse Event reporting
- Advise clinical centers on general clinical safety issues

2.1.6 Diet Committee

Function of the Diet Committee:

- Review ongoing data collection with regard to issues of completeness and accuracy.
- Respond to field questions and revise data collection procedures as necessary.
- Develop plans for interim data analysis: general descriptive statistics, comparisons across sites, trends over time.
- Develop plans for continuing training efforts of new staff.
- Identify and recommend solutions to issues regarding the pooling of nutritional data across sites.
- Monitor protocol compliance with respect to samples for serum 25 hydroxyvitamin D in early infancy, vitamin E, anti-oxidants (e.g., carotenoids, ascorbic acid, selenium, or omega-3 fatty acids).

2.1.7 Environmental Exposures Committee

Function of the Environmental Exposures Committee:

- Monitor data collection for increased exposure to routine childhood immunizations and their timing; environmental factors that may be contained in drinking water (e.g., low concentrations of zinc or high concentrations of nitrates, or lower pH levels); exposure to household pets, various allergies; and excessive weight gain.

2.1.8 Genetics Committee

Function of the Genetics Committee:

- Review accumulating data and suggest descriptive analyses: prevalence estimates in relatives and general population, differences by geographic site, etc.
- Develop parameters to assess and monitor HLA reference lab performance.
- Review data produced by HLA reference lab with respect to comparisons with screening labs, frequencies of higher resolution typing.

- Identify a professional genetic counselor or medical geneticist at each clinical site and provide recommendations for uniform training on the TEDDY study.

2.1.9 Human Subjects/Publicity/Publications Committee

Function of the Human Subject/Publicity/Publications Committee

- Develop, a standard protocol to be used to inform parents of the presence of persistent autoimmunity and its associated increased risk for T1DM in the child.
- Provide TEDDY oversight for the distribution of study related materials from each clinical site.
- Develop a task list and provide direction to Matthews Media group for the development of materials for TEDDY.

2.1.10 Immune Markers Committee

Function of the Immune Markers Committee

- Develop parameters to assess and monitor antibody lab performance.
- Review TEDDY study data collection and hypotheses specifically regarding exposures that may lead to the promotion of Type 1 diabetes among those who are antibody positive.
- Review and recommend to PI Committee other markers of inflammation that should be measured and monitored in the antibody positive population.

2.1.11 Infectious Agents Committee

Function of the Infectious Agents Committee

- Develop parameters and monitor protocol compliance with respect to collection of stool samples.
- Monitor compliance and results of RNA extraction.
- Design an approach towards interim analysis of samples to ensure quality and yield.

2.1.12 Laboratory Implementation Committee

Function of the Laboratory Implementation Committee

- Review/resolve ongoing issues associated with the implementation of all laboratory procedures for the TEDDY study.
- Coordinate/implement protocol decisions made by other relevant committees such as the Genetics, Diet, and Immune Markers committees.
- Review/implement the QA/QC protocols associated with laboratory work with consult from other appropriate committees as needed.

2.1.13 Maternal Studies Committee

Function of the Maternal Study Committee:

- Monitor enrollment and compliance with respect to sample submission of mothers into the study during pregnancy.

2.1.14 Psychosocial Committee

Function of the Psychosocial Committee:

- Review and monitor compliance/quality of psychosocial data collection efforts.
- Develop questions to add to the parental/primary caretaker's annual assessment that address the parent's or primary caretaker's perceptions of the child's function and well-being (e.g., does the caretaker overprotect, stigmatize or treat the child differently because the child is at-risk for diabetes) at 39 months.
- Provide appropriate guidelines for referral as per protocol if the mother answers #10 affirmative or gets a total score of ≥ 13.

2.1.15 Quality Assurance Committee

Function of the Quality Assurance Committee:

- Has overall responsibility for the oversight of QC policies and procedures. This committee will rely on the scientific expertise of the appropriate TEDDY committees in carrying out this responsibility.
- The QC Committee will develop appropriate reports and documentation for circulation to the Steering Committee and the External Advisory Board.

2.1.16 Study Coordinators Committee

Function of the Study Coordinators Committee:

- Develop and update the TEDDY Manual of Operations in coordination with the DCC.
- Provide a forum for study coordinators to address questions regarding the logistics of the TEDDY study.
- Provide discussion of common concerns regarding subject screening and retention issues.

2.2. Study Units

2.2.1. Data Coordinating Center (DCC)

The Data Coordinating Center is responsible for all data management and statistical considerations for TEDDY. The DCC has both administrative and scientific functions. The administrative functions include providing for central registration of all subjects enrolled in the study; preparation of data management

aids; maintaining subject and protocol files; providing statistical reports on progress of study at all meetings; preparing quality control reports; reimburse clinical centers for recruitment and subject participation; and serving on all TEDDY administrative committees. Scientific functions include review of all proposed protocols and development of statistical design for the study; analysis of study results; review of all manuscripts for statistical considerations; development and testing of predictive models for disease progression; and conduct of statistical research concerning intervention trials in IDDM.

2.2.2. Clinical Centers

The Clinical Centers are responsible for implementation of the protocols of TEDDY, including screening of potential subjects, enrollment of subjects, and conduct of the Protocol. Each Clinical Center will have a Principal Investigator, a full time study coordinator, other investigators, and ancillary personnel as needed. The Principal Investigator will work with the Data Coordinating Center, Steering Committee, and NIH Staff assigned to this project to conduct the study in accordance with the Protocol and Manual of Operations. The Clinical Centers are expected to meet the patient recruitment goals as specified by the Protocol and will work with the DCC, and all Core Laboratories to reach study goals and maintain quality of the data. In addition, each Clinical Center may have collaborating institutions.

2.2.3. Reference Laboratories

There will be various types of reference laboratories. These are responsible for measurement of the critical variables in the study protocol. The reference laboratories include:

2.2.3.1. Autoantibody Reference Laboratories

Dr. Liping Yu's lab (previously Dr. George Eisenbarth's lab) at the Barbara Davis Center for Childhood Diabetes will serve as the North American autoantibody reference lab. Dr. Kathleen Gillespie's lab (previously Alistair Williams' lab and Dr. Polly Bingley's lab) at Bristol University will serve as the European autoantibody reference lab. They will serve as the central laboratories for measurement of serum IAA, IA-2 and GAD_{65} autoantibodies. The Barbara Davis Center for Childhood Diabetes will also measure ZnT8A on selected positive antibody samples (as determined by the Immune Markers committee) for both US and European subjects. The labs will conduct a standardization and proficiency program for the autoantibodies. They will also be responsible for the storage of serum samples.

2.2.3.2. Genetics Laboratory

Dr. Henry Erlich's lab at the Children's Hospital Oakland Research Institute will serve as the central genetics reference laboratory for the testing of genetic results. They will be responsible for verifying DRB1-DQA1-DQB1 haplotypes on subjects identified for intensive follow-up, performing more

complete HLA typing at loci outside of this core haplotype such as HLA-A, HLA-B and DPB1, and storing samples sent from the clinical centers. The reference laboratory must initially achieve certification through the CDC proficiency testing program, and must maintain annual certification.

2.2.3.3. RNA Laboratory

Dr. Jin-Xiong She's lab at Georgia Regents University will serve as the RNA extraction lab. They will be responsible for the extraction of RNA from whole blood and sending it to the NIDDK repository for storage.

2.2.3.4. HbA1c Laboratory

Dr. Randie Little's lab at the University of Missouri will serve as the HbA1c lab. They will be responsible for the measurement of HbA1c samples sent from the TEDDY Clinical Centers.

2.2.3.5. OGTT Laboratory

Dr. Santica Marcovina's lab at the University of Washington served as the OGTT lab through 2020. In September 2020 Dr. William Winter's lab at the University of Florida became the OGTT lab for TEDDY. They will be responsible for the measurement of insulin, glucose and c-peptide samples sent from the TEDDY Clinical Centers.

2.2.3.6. Thyroid Antibody Laboratory

Dr. William Winter's lab at the University of Florida will serve as the Thyroid Antibody Lab. They will be responsible for the measurement of thyroid peroxidase (TPOA) and thyroglobulin (ThGA) on samples sent from the TEDDY Clinical Centers. Samples from children positive for either thyroid antibody will also be tested for TSH in the same sample.

2.2.4. Central Repository

The NIDDK Bio-sample, and Genetics Repositories will store samples during the study that will be analyzed at the end of the study for the case-control analysis.

Appendix

TEDDY ANCILLARY STUDIES DEFINITION AND GUIDELINES

Introduction

TEDDY Study data and the biosample repository are valuable resources for the investigation of type 1 diabetes etiology and pathogenesis. The use of this material for TEDDY investigators is determined by TEDDY leadership through its committees and as a result of manuscript proposals which are reviewed and approved by the TEDDY Publications and Presentations Committee. These, collectively, are called TEDDY studies. Proposals from investigators who do not wish to work within this framework are called ancillary studies.

Ancillary studies will be evaluated with careful consideration of their potential impact on the objectives and performance of the TEDDY Study. Studies that complement the objectives and thereby enhance the value of the TEDDY Study are strongly encouraged. These studies however, must not interfere with the continued interest and participation of the study subjects and investigators. To protect the interests of the TEDDY Study, each ancillary study proposal must be individually reviewed and approved by the TEDDY Ancillary Studies Committee before its initiation. All approved ancillary studies will be reviewed by the Ancillary Studies Committee yearly for progress and impact on the TEDDY Study as a whole.

The TEDDY Study has adopted policies and procedures in support of its commitment to sharing data with the scientific community while also protecting the privacy of participants. In accordance with the TEDDY Data Sharing Policy, data are made publicly available via designated controlled-access data repositories. Investigators are encouraged to determine if the TEDDY study data they are seeking can be directly requested from designated NIH Data Repositories. If the desired data is available through the NIH Data Repositories, then an investigator does not need to submit a TEDDY ancillary study proposal and can move forward with seeking approval and data directly from the appropriate NIH Data Repository.

Ancillary Study Definition

An ancillary study is defined as externally funded (not TEDDY-funded) research involving TEDDY Study subjects' data that is not currently available through the NIH Data Repositories (see section below for more details) and/or samples. The investigator for the conduct of the ancillary study is a partner in the TEDDY Study and is therefore obliged to follow the rules and regulations governing the study as defined in the study protocol and by the Steering Committee.

Before submitting a TEDDY ancillary study proposal, the investigator should first confirm if the desired data is or is not already publicly available via the designated controlled-access data repositories (if the desired data is available through the NIH Data

Repositories, a TEDDY ancillary study proposal is not needed). TEDDY data are submitted to designated public NIH Data Repositories in segments that reflect the study's progress. These data releases are submitted at different time points and to various repositories, depending on funding agency requirements and the nature of the data. Please see links below for more detailed information.

- TEDDY NIH Data Repository Submissions
- Data Request Instructions
  - The database of Genotypes and Phenotypes (dbGAP)
  - The NIDDK Central Repository
  - The Sequence Read Archive (SRA)
  - The Metabolomics Workbench

If the data being requested is not available through the NIH Data Repositories:

Regardless of the funding status of the proposed study, if the proposal requires TEDDY Data Coordinating Center (DCC) input, then it will be considered an ancillary study subject to all TEDDY policies and procedures, including those of the TEDDY Publications and Presentations Committee. The TEDDY DCC will charge $250 per hour plus 50% indirect costs for time spent on preparation of the data.

If biological samples are being requested:

1. If the proposal has already received external funding, the investigator should contact the TEDDY DCC at TEDDY@epi.usf.edu to request the samples. The proposal will not be reviewed by the Ancillary Studies Committee as it has already been reviewed and approved by the funding agency. The TEDDY DCC will charge $250 per hour plus 50% indirect costs for time spent on identification of samples and communication with the Fisher BioServices Sample Repository. The Fisher BioServices Sample Repository will charge $12.30 per sample for pulling and aliquoting (minimum charge per order $397.36), or if the ancillary study does not require aliquoting, $8.47 per sample for pulling (minimum charge per order $365.80); the ancillary study will be responsible for all shipment costs from the Repository to the ancillary study lab.

2. If the proposal has not already received external funding, the investigator should submit the proposal to the TEDDY DCC at TEDDY@epi.usf.edu. The TEDDY Ancillary Studies Committee will examine the proposal and provide feedback if the samples requested are available. The TEDDY DCC will charge $250 per hour plus 50% indirect costs for time spent on identification of samples and communication with the Fisher BioServices Sample Repository. The Fisher BioServices Sample Repository will charge $12.30 per sample for pulling and aliquoting (minimum charge per order $397.36) or if the ancillary study does not require aliquoting, $8.47 per sample for pulling (minimum charge per order $365.80); the ancillary study will be responsible for all shipment costs from the Repository to the ancillary study lab.

Reasons for Required Approval of Ancillary Studies

Investigators and subjects are entitled to prior assurance that all ancillary studies are of high scientific merit and that no ancillary study will:

1. Cause a deviation from the defined study protocol.
2. Complicate the interpretation of the study results.
3. Potentially adversely affect subject cooperation or interest in the study.
4. Jeopardize the public image of the study.
5. Create a significant diversion of study resources locally or at the coordinating center or any other unit.
6. In any way negatively influence the cooperative spirit of the collaborating investigators.
7. Require use of samples for a study of low priority as deemed by the Steering Committee.
8. Otherwise compromise the scientific integrity of the study.

Review by the Ancillary Studies Committee

All proposed ancillary studies will be submitted to the TEDDY DCC which will coordinate its review by the TEDDY Ancillary Studies Committee. The DCC, in consultation with the Chair of that committee, will identify at least two reviewers with such expertise as may be necessary if not already represented by the membership of the Ancillary Studies Committee. It will arrange for reviews and conference calls of committee members to discuss any proposed study. The Ancillary Studies Committee shall vote on the proposed ancillary study.

Funding for Ancillary Studies

The TEDDY Study does not provide funds for ancillary studies. If funds are needed, the investigator must explore other avenues such as submission of a research grant application, or use other sources of funds, i.e., foundations. The source and amount of anticipated funds must always be identified in an application to the Ancillary Studies Committee.

The ancillary study applicant should be aware that both the aliquoting and shipping of biological samples and the provision of data cannot be provided free of charge. The cost rates of these services must be taken into account in the application for external funding. The Fisher BioServices Sample Repository will charge $12.30 per sample for pulling and aliquoting (minimum charge per order $397.36) or if the ancillary study does not require aliquoting, $8.47 per sample for pulling (minimum charge per order $365.80). The ancillary study applicant will be responsible for all shipment costs from the Repository to the ancillary study lab. The TEDDY DCC will charge $250 per hour plus 50% indirect costs for time spent on identification of samples and/or preparation of data for the ancillary study.

Preparation of Proposals for Ancillary Studies Committee Review

The proposal submitted to the Ancillary Studies Committee should follow the National Institutes for Health (NIH) research grant (R01) format.

1. It should include a description of the objectives, methods, significance and plans for analysis.
2. If TEDDY samples are being requested, the type of sample, required volume and timepoints should be specified in the proposal.
3. The proposal should discuss the measures to be taken to ensure subject safety and confidentiality, and a statement by the investigator on the potential impact of the ancillary study on the TEDDY Study trial.
4. If applicable, prior approval by the appropriate Human Subjects Committee should be demonstrated.
5. Information regarding the source of funding should be provided in the proposal. It should clearly indicate the resources available for this study. If resources are being sought from granting agencies this must be indicated in the application.

To facilitate the review of the proposal the investigator should specifically address each of the following points, which will be examined in detail. Responses must be clearly delineated in a document that is separate from the formal grant proposal:

1. The scientific merit of the proposal and the potential contributions that the proposal will make to the TEDDY Study.
2. That the ancillary study does not cause a deviation from the defined study protocol.
3. That the proposed study does not complicate the interpretation of the results of the TEDDY Study.
4. That it does not adversely affect subject cooperation and participation.
5. That the volume of whole blood or sera taken from subjects does not exceed safe or prudent limits.
6. That the proposed study does not create a significant diversion from the TEDDY Study.
7. That the study does not divert or expend resources from the TEDDY Study either locally or at the DCC.
8. That the study does not adversely influence the cooperative spirit of the collaborating investigators.
9. That the study does not compromise the scientific integrity of the TEDDY Study.
10. That adequate resources are available to complete the proposed study or are requested from granting agencies.
11. That techniques and assays essential to the study are well established in the laboratory.
12. Results of ancillary studies will not be revealed to either TEDDY Study participants or their clinical team unless as called for in the description of the proposal.

Finally, a yearly report summarizing study progress, results, and the impact of the ancillary study on the TEDDY Study will be submitted to the TEDDY Ancillary Studies Committee and the TEDDY Steering Committee and reviewed every 12 months for continued approval by TEDDY.

Procedures for Obtaining Approval

The investigator should submit their ancillary study proposal to the DCC at the University of South Florida (TEDDY@epi.usf.edu) which will then distribute it to the Ancillary Studies Committee. To ensure a thorough scientific review the Chairman of the Ancillary Studies Committee may elect to seek outside expert opinion in advance to the committee meeting, as described above. A simple majority vote constitutes an approval by the Ancillary Studies Committee when a quorum of at least 4 members is present. The investigator will be notified within one week of the meeting of the approval status of his/her proposal.

Publication of Approved TEDDY Ancillary Studies

In accordance with TEDDY's Publications and Presentations Policies, all manuscripts written by ancillary study investigators should be submitted to the DCC to be reviewed for appropriate study attribution and acknowledgment prior to journal submission. Any ancillary study manuscript, abstract, presentation, or press release must acknowledge that the TEDDY Study Group is funded by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (NIDDK-NIH) using the following statement:

"The TEDDY Study is a collaborative clinical study funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases (NIAID), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institute of Environmental Health Sciences (NIEHS), Centers for Disease Control and Prevention (CDC), and JDRF. This manuscript was not prepared in collaboration with the investigators of the TEDDY Study Group and does not necessarily represent the official views of the TEDDY Study or the National Institutes of Health."

Non-ancillary Studies

Studies that can obtain needed data from the NIH Data Repositories are not considered ancillary studies, unless the investigator chooses to submit the proposal for TEDDY review. Any study requiring TEDDY Data Coordinating Center assistance in the design, analysis, planning, or requests data from the DCC, is regarded as an ancillary study, subject to TEDDY policies and procedures. Studies needing samples must work with the DCC, since the samples are available only through the DCC. If the request is more than sample identification and availability, then the proposal will also be considered an ancillary study, subject to the aforementioned policies.

Return of samples to the Fisher BioServices Sample Repository

Once analyses are completed, the ancillary study should return any leftover biological samples to the Fisher BioServices Sample Repository. The ancillary study should contact the DCC (TEDDY@epi.usf.edu) for information on returning the samples.

3. Contact Information

3.1. TEDDY Web Site:

http://teddy.epi.usf.edu/

3.2. Data Coordinating Center (DCC):

Jeffrey P. Krischer, Ph.D.
University of South Florida
Health Informatics Institute
3650 Spectrum Blvd; Suite 100
Tampa, Florida 33612
Email: Jeffrey.Krischer@epi.usf.edu
Ph: 813-396-9501 Fax: 813-396-9601

3.3. NIDDK Bio-Sample Repository:

Fisher Bioservices Corporation
NIDDK Biorepository
20301 Century Blvd.
Building 6, Suite 400
Germantown, Maryland 20874
Lab-shared Email: BIO-NIDDKRepository@thermofisher.com
Ph: 240-686-4702 Fax: 301-515-4049

3.4. National Institutes of Health:

Beena Akolkar, Ph.D.
Diabetes, Endocrinology & Metabolic Disease
Two Democracy Plaza, MSC 5460
6707 Democracy Plaza, Room 681
Bethesda, Maryland 20892
Email: akolkarb@extra.niddk.nih.gov
Ph: 301-594-8812 Fax: 301-480-3503

3.5. Clinical Centers:

3.5.1. Pacific Northwest Diabetes Research Institute

William A. Hagopian, M.D., Ph.D.
Diabetes Department
720 Broadway
Seattle, Washington 98122
Email: wah@uw.edu
Ph: 206-860-6759 Fax: 206-320-1448

3.5.1.1. Visit Locations:

- Pacific Northwest Research Institute Clinics
- North Washington Clinics

- South Washington Clinics

3.5.2. Lund University

Åke Lernmark, M.D., Ph.D.
Department of Clinical Sciences
Clinical Research Centre, Lund University
Hus 60, plan 11
Box 50332
SE-20502 Malmö, Sweden
Email: ake.lernmark@med.lu.se
Ph: +46 40 39 19 01 Fax: +46 40 39 11 22

3.5.2.1. Visit Locations:

- University Hospital MAS
  TEDDY Clinic
  Department of Internal Medicine
  Wallenberglaboratory, Ing 46, Plan 2
  SE-90501 Malmö, Sweden
  Ph: +46 40 33 23 90 Fax: +46 40 33 70 41
- Helsingborgs Lasarett
- Kristianstads Centralsjukhus

3.5.3. University of Colorado Health Science Center

Marian J. Rewers, M.D., Ph.D.
Barbara Davis Center
1775 N. Aurora Street, Mail Stop A140
P.O. Box 6511
Aurora, Colorado 80045-6511
Email: marian.rewers@cuanschutz.edu
Ph: 303-724-6757 Fax: 303-724-6787

3.5.3.1. Visit Locations:

- BDC Clinic
- Exempla Good Samaritan Hospital
- Exempla Lutheran Hospital
- Exempla St. Joe's Hospital
- Rose Medical Center
- TEDDY/DAISY Clinic
- Swedish Medical Center
- Aurora South Medical Center
- Presbyterian – St. Lukes Medical Center
- Sky Ridge Medical Center
- UCH – Maternal Fetal Clinic
- Avista Adventist Hospital
- Parker Adventist Hospital

- North Suburban MC
- Littleton Adventist Hospital
- Presbyterian/St. Luke's Medical Center

3.5.4. Turku University Central Hospital

Jorma Toppari, M.D., Ph.D.
Department of Pediatrics
Kiinamyllynkatu 4-8
Turku, Finland 20520
Email: jorma.toppari@utu.fi
Ph: +358 2 333 51 Fax: +358 2 313 3491

3.5.4.1. Visit Locations:

- Tampere University Hospital, Department of Pediatrics
  DIPP Clinic, Finn-Medi 3, 1st Floor
  Biokatu 10
  FIN-33520 Tampere
  Finland
  Ph:+358 3 311 611 Fax: +358 3 215 8420

- Turku University Central Hospital, Department of Pediatrics
  DIPP Clinic, Data-City Bldg, 5th floor
  Lemminkaisenkatu 14-18A
  20520 Turku
  Finland
  Ph: +358 2 313 3000 Fax: +358 2 313 3491

- University of Oulu, Department of Pediatrics
  DIPP Clinic, Research Laboratory
  Kajaanintie 52 A6, L514
  FIN-90220 Oulu
  Finland
  Ph: +358 8 315 5384 Fax: +358 8 315 5559

3.5.5. Augusta University

Richard McIndoe, Ph.D.
Center for Biotechnology and Genomic Medicine
1120 15th Street, CA4124
Augusta, Georgia 30912-2400
Email: rmcindoe@augusta.edu
Ph: 706-721-3410 Fax: 706-721-3688

3.5.5.1. Visit Locations:

- Medical College of Georgia Health Inc. (Augusta, GA)
- Trinity Hospital (Augusta, GA) – previously St. Joseph Hospital

- University Hospital (Augusta, GA)
- MCG Consultation Room (Augusta, GA)
- Northside Hospital (Atlanta, GA)
- Piedmont Hospital (Atlanta, GA)
- Atlanta Clinic (Atlanta, GA)
- Kennestone Hospital (Atlanta, GA)
- Shands Hospital at the University of Florida (Gainesville, FL)
- North Florida Regional Medical Center (Gainesville, FL)
- Shands at Alachua General Hospital (Gainesville, FL)
- UF Clinic (Gainesville, FL)

3.5.6. Institute of Diabetes Research, Helmholtz Zentrum München, and Klinikum rechts der Isar, Technische Universität München, and Forschergruppe Diabetes e.V.

Anette G. Ziegler, M.D.
Ingolstaedter Landstrasse 1
85764 Neuherberg, Germany
Email: anette-g.ziegler@helmholtz-muenchen.de
Ph: 0049-3079-3114 Fax: 0049-89-3081733

3.5.6.1. Visit Locations:

- Diabetes Research Institute Clinics

3.6. Reference Labs:

3.6.1. European Autoantibody Reference Lab

University of Bristol - Diabetes and Metabolism
Kathleen Gillespie
Learning and Research Building
Southmead Hospital
Bristol, BS105NB United Kingdom
Email: K.M.Gillespie@bristol.ac.uk
Ph: 441174148058

3.6.2. US Autoantibody Reference Lab

Barbara Davis Center for Childhood Diabetes
Liping Yu, Ph.D.
M20-4201E
1775 Aurora Ct, UC Denver, AMC
Aurora, CO 80010
Email: Liping.Yu@cuanschutz.edu
Ph: (303) 724-6809

3.6.3. HLA Reference Lab

Up until April 2017
Children's Hospital Oakland Research Institute
Henry Erlich, Ph.D.
5700 Martin Luther King Jr. Way
Oakland, CA 94609
Email: Henry.Erlich@roche.com
Ph: (510) 814-2918

From April 2017 and on
Pacific Northwest Diabetes Research Institute
William A. Hagopian, M.D., Ph.D.
Diabetes Department
720 Broadway
Seattle, Washington 98122
Email: wah@uw.edu
Ph: 206-860-6759 Fax: 206-320-1448

3.6.4 RNA Reference Lab

Jinfiniti Biosciences
Jin-Xiong She, Ph.D.
Center of Innovation for Life Sciences
Georgia Regents University
1120 15th Street, CA 2105
Augusta, Georgia 30912-7624
Email: jshe@gru.edu
Ph: 706-721-4161 Fax: 706-721-3688

3.6.5 HbA1c Lab

University of Mo-Columbia
Randie Little, Ph.D.
Department of Pathology and Anatomical Sciences
1 Hospital Dr Rm M767
Columbia, MO 65212
Email: LittleR@health.missouri.edu
Ph: (573) 882-1257 Fax: (573) 884-8823

3.6.6 OGTT Lab

Up until May 2020
University of Washington
Santica Marcovina, Ph.D., Sc.D.

Northwest Lipid Metabolism and Diabetes Research Laboratories
401 Queen Anne Ave North
Seattle, Washington 98109
Email: smm@uw.edu
Ph: 206-685-3331

From May 2020 and on
University of Florida
William Winter, M.D.
UFHPL Endocrine Lab
4800 SW 35 Drive
Gainesville, FL 32608
Email: winter@pathology.ufl.edu
Ph: 352-265-9900

3.6.7 Cortisol Lab

Linkoping University Hospital
Srinivas Uppugunduri, PhD
Division of Clinical Chemistry
House 448 floor 11
SE58185 Linkoping, Sweden
Email: Srinivas.Uppugunduri@lio.se
Phone: +46-101033958

3.6.8 Thyroid Lab

University of Florida
William Winter, M.D.
UFHPL Endocrine Lab
4800 SW 35 Drive
Gainesville, FL 32608
Email: winter@pathology.ufl.edu
Ph: 352-265-9900

4. Policies

4.1. IRB Approval

All TEDDY Study Sites must have Institutional Review Board (IRB) approval, prior to their initiation as required by the national statutes and good clinical practice. If requested, the IRB will be given the opportunity to monitor the progress of the studies. For Clinical Centers, this must be their own local IRB. All IRB Approval Letters and approved Consent Forms must be kept on file at both the DCC and the Clinical Center. Affiliates and Satellites should send copies of same to their Clinical Center, who are responsible for maintaining Center files and for forwarding copies to the DCC. All IRB annual reports, IRB re-approval letters, and updated Consent Forms (with date clearly marked) must be kept on file at the Clinical Centers and the DCC.

4.2. Informed Consent Forms

A two-step consent process will be used. The first consent will be specific for screening newborns for high-risk genotypes at the HLA and other loci in the general population or in families having a first-degree relative affected with T1DM (Phase 1). The second consent will cover procedures that will be used in the follow-up of the risk for T1DM (Phase 2).

TEDDY study coordinators or investigators at each site will administer the Informed Consent Forms. Each study participants' parents/guardians will have sufficient time to fully read the Consent Forms and have any questions answered. They will be told that they can take the Consent Forms home and request consultation with other individuals. It will be explained to them that there will be separate consent for each phase of the study and that consent for Phase 1 of TEDDY does not mean consent for further participation in other TEDDY studies, ancillary studies or potential intervention trials. Additional consent will be required.

Model Consent Forms are provided in Sections 5 (screening) and 7 (follow-up) of the Manual of Operations. These may be modified to conform with local IRB requirements.

4.3. Gender and Ethnic Diversity

Both boys and girls, and members of all racial and ethnic populations of the United States, Finland, Germany and Sweden will be screened. The distributions of gender, race, and ethnic group will be monitored and reported annually to the TEDDY Steering Committee. If the study population does not reflect recruitment targets, corrective actions will be taken.

4.4. Confidentiality

Personal information that is obtained for TEDDY will be maintained in distinct databases at each TEDDY Clinical Center. The personal data will be kept separate from study data obtained during the TEDDY Study at the local TEDDY Clinical Center. All information obtained from this study will be identified with a unique study number, and will not be kept with the participant's name. Data from TEDDY examinations and procedures will be sent to the TEDDY Data Coordinating Center. This information will be entered into a database that will be used for statistical analysis. The Data Coordinating Center will not receive any personal information on study participants.

Samples collected will be primarily stored at the local TEDDY Clinical Centers or at the NIDDK central repository. The stored samples may be used by TEDDY investigators to further characterize factors predicting risk of developing T1DM. All samples will be coded with a unique study number. Linkage of the unique study number to the names of the participants will be maintained at the local TEDDY Clinical Center. However, the names of participants will not be disclosed to any of the TEDDY investigators or to any other individuals except for informing participants' parents/guardians of test results or possible participation in future studies. If such disclosure is requested for specific research or other purposes, approval by the TEDDY Steering Committee will be required. To further ensure privacy, a Certificate of Confidentiality will be obtained for the study by the TEDDY Data Coordinating Center. An explanation of the Certificate of Confidentiality is included in the Consent Forms.

4.5. Certificate of Confidentiality

Certificates of Confidentiality have been granted by the U.S. Department of Health and Human Services to allow TEDDY investigators to protect and maintain the privacy of TEDDY study records, which potentially might affect a subject's insurability. These certificates state that, "In accordance with the provisions of section 3019(d) of the Public Health Service Act 42 U.S.C. 241(d) this Certificate is issued to protect the privacy of research subjects by withholding their identities from persons not connected with the research. Persons so authorized to protect the privacy of such individuals may **not** be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals." All sites should be cautious about hospital and/or GCRC records. These may inadvertently be released if sought separately.

4.6. Scientific Integrity

All members of the TEDDY Study Group recognize there is an ethical responsibility at all levels of clinical research--from data collection and reporting to overall study conduct. In order to ensure the integrity of clinical research as well as to comply with federal requirements, the policy of the TEDDY study shall be to maintain objectivity

in research, protect patient safety, and uphold the public trust. The research data generated by TEDDY must, thus, meet high quality standards and be reliable, verifiable and reproducible; and research records of all types must accurately reflect the data as recorded in the primary patient record. Scientific misconduct is unacceptable and must be reported. Misconduct means fabrication, falsification, plagiarism, or other dishonest practices that seriously deviate from those that are commonly accepted within the scientific community for proposing, conducting or reporting research. It does not include honest errors or honest differences in interpretation or judgments of data. Completion of Scientific Integrity Forms is required for all members of the Study Group, including those at Affiliates and Satellites.

4.7. Duality of Interest

The scientific credibility and the general acceptance of the results of a research study clearly depend, in part, on the integrity and objectivity of the investigators involved in the study, and even the perception that an investigator has a bias can cast doubt on the validity of the results. The presence of dualities of interest may suggest or give the appearance of a bias. Such dualities of interest may arise from interactions between TEDDY investigators and other organizations such as private corporations, scientific or medical societies and non-profit organizations. Accordingly, the study group must take care that interactions and/or relationships with industry or other groups outside of the study organization (defined to include competing scientific/treatment protocols) are not allowed to influence, or appear to influence, the objectivity of the decision making process in any manner. While dualities of interest are not prohibited, it is imperative that real, possible, or potential dualities be declared to ensure objectivity and maintenance of individual and organizational integrity. While the process utilized to develop the TEDDY protocol should diffuse the potential impact of any duality that exists for an individual member of the Research Group, it is the position of TEDDY that disclosure of any duality that exists or arises for a member of the Research Group will assure that TEDDY has been conducted in a fair and scientifically sound manner, devoid of inappropriate influences or the appearance of inappropriate influences. This policy and accompanying procedures were established to address such concerns as they relate to members of TEDDY. This statement defines duality of interest and related terms and identifies when disclosure is appropriate. Corporate support provided to the overall study is not addressed herein, but is addressed in specific letters of agreement between the study chairman and the corporate entities.

Completion of Duality of Interest Forms is required for all members of the Study Group who participate in the decision making process, i.e. members of any committee, monitoring group, etc. These forms should be voluntarily updated as soon as significant changes in duality of interest occur and reviewed/updated by all investigators annually.

4.8. Protocol Changes

Adoption of changes to the approved TEDDY Protocol require action by a supermajority (67%) vote of the Steering Committee. Notice of all Steering Committee meetings must specifically reference the adoption of any TEDDY Protocol changes, if such are to be on the agenda. Adoption of any changes to the approved TEDDY Protocol may not arise from the floor. Seventy-five percent (75%) of the voting membership of the Steering Committee constitutes a quorum for consideration changes to the approved TEDDY Protocol. NIH Project Officer must review adoption of any changes to the approved TEDDY Protocol.

4.9. Qualification for Additional TEDDY Studies

All individuals participating in the TEDDY Study will be eligible for consideration for participation in other studies as those studies become available. These studies may include prevention trials in individuals who have not progressed to T1DM, intervention trials in individuals who progress to T1DM while in the TEDDY Study, and ancillary studies requiring additional data beyond that to be collected for this protocol. Participants of the TEDDY Study, who subsequently enter intervention trials, will be advised that they continue to contribute data toward the TEDDY study if they do not specifically wish to be withdrawn from the TEDDY study. In all cases of new studies, eligibility will require that the inclusion and exclusion criteria specific to those studies be met.

5. Screening Recruitment

5.1. Screening plan

Purpose: To identify newborn children with elevated risk for type 1 diabetes mellitus (T1DM) based on HLA genetic markers from the general populations of newborns and among newborns with a first degree relative with T1DM.

Each TEDDY clinical site is responsible for screening a portion of newborns during the study's five-year screening period. A proportion of those screened will be identified as having the higher risk genes and will therefore be eligible for participation in the prospective follow up study. The approach to screening varies between the clinical centers and will be indicated below and detailed in Appendix A1-6 for each Clinical Center.

The approximate number of higher risk children identified will also vary by site and is detailed in Table 5.1.

Screening began September 1, 2004 and will last for 5 years. The anticipated rate of screening enrollment and identification of eligible subjects is as follows:

Table 5.1: Number Screened, Number of Eligible Newborns and Number Enrolled by Clinical Center

	Screening/year for remaining 3 years of accrual		Eligible/year for remaining 3 years of accrual				Enroll/year for remaining 3 years of accrual			
Center	General Population	FDR	Eligibility Rate GP	General Population	Eligibility Rate FDR	FDR	Enrollment Rate GP	General Population	Enrollment Rate FDR	FDR
Colorado	16,316	176	5.1%	832	23.5%	41	42%	350	64%	26
Finland	11,204	132	5.6%	627	35.1%	46	44%	276	60%	28
Georgia/Florida	14,272	172	3.5%	500	16.4%	28	33%	165	50%	14
Germany	7,296	356	3.9%	285	19.5%	69	30%	85	80%	56
Sweden	8,956	220	7.6%	681	18.3%	40	65%	442	65%	26
Washington	23,628	204	3.9%	921	26.7%	54	37%	341	75%	41

State										
TOTAL:	81,672	1,260		3,846		278		1659		191

	Actual total screened by site for first 2 years of accrual		Projected total screened by site for remaining 3 years of accrual		Total screened by site for 5 years of accrual	
Center	**General Population**	**FDR**	**General Population**	**FDR**	**General Population**	**FDR**
Colorado	17,896	296	48,948	528	66,844	824
Finland	22,827	271	33,612	396	56,439	667
Georgia/Florida	25,204	226	42,816	516	68,020	742
Germany	6,695	526	21,888	1,068	28,583	1,594
Sweden	17,991	358	26,868	660	44,859	1,018
Washington State	20,363	139	70,884	612	91,247	751
TOTAL:	110,976	1,816	245,016	3,780	355,992	5,596

	Actual total eligible by site for first 2 years of accrual		Projected total eligible by site for remaining 3 years of accrual		Total eligible by site for 5 years of accrual	
Center	**General Population**	**FDR**	**General Population**	**FDR**	**General Population**	**FDR**
Colorado	811	66	2,496	123	3,307	189
Finland	1,254	94	1,881	138	3,135	232
Georgia/Florida	824	34	1,500	84	2,324	118
Germany	244	99	855	207	1,099	306
Sweden	1,282	61	2,043	120	3,325	181
Washington State	635	28	2,763	162	3,398	190
TOTAL:	5,050	382	11,538	834	16,588	1,216

	Actual total enrolled by site for first 2 years of accrual		Projected total enrolled by site for remaining 3 years of accrual		Total enrolled by site for 5 years of accrual	
Center	**General Population**	**FDR**	**General Population**	**FDR**	**General Population**	**FDR**
Colorado	262	35	1,050	78	1,312	113
Finland	556	43	828	84	1,384	127
Georgia/Florida	204	15	495	42	699	57
Germany	72	69	255	167	327	236
Sweden	796	40	1,326	78	2,122	118
Washington State	146	14	1,023	123	1,169	137
TOTAL:	2,036	216	4,977	572	7,013	788

	General Population actual total for first 2 years of accrual	FDR actual total for first 2 years of accrual	General Population projected total for remaining 3 years of accrual	FDR projected total for remaining 3 years of accrual	Total
Screened	101,612	1,703	245,016	3,780	352,111
Follow-up Eligible	5,050	382	11,538	834	17,804
Enroll	2,036	216	4,977	572	7,801

*First Degree Relative

The five year goal is to recruit a total of 7,800 children to be followed for 15 years (Table 5.2). The expected number of cases with autoantibodies and eventually developing T1DM are also shown in Table 5.2.

Table 5.2: Anticipated Total Study Accrual and Response Rates for each cohort over 5 years

Over 5 years	General Population	FDR
Enroll	7,013	788
Cases - autoantibodies by age 6	281 (4%)	105 (13.3%)
Cases - T1DM by age 15	281 (4%)	105 (13.3%)

5.2 Screening Eligibility Criteria: General Population & FDR

Infants are eligible for screening if they:

- Are less than 4 months of age.
- Have a parent or primary caretaker who has given informed consent for screening.
- Have a parent or primary caretaker for US sites who has signed a HIPAA authorization permitting the use of protected health information for this research purpose, if required by the sites local IRB.

Additional FDR-specific eligibility criteria:

Initial eligibility for the FDR cohort requires that the infant has a first degree relative with T1DM. This includes biological mother, father, or sibling. A biologically related half sibling alone does not meet this criterion. An infant who's only relative with T1DM is a half sibling would qualify for the general population cohort screening.

If at any time during the subject's participation there is a change in the subject's family history of Type 1 Diabetes (first degree relative has just developed T1D, first degree relative has just found out that they have T1D, it is discovered that a mistake was made in the reporting of the T1D status of a first degree relative, etc) the clinical center should be sure to update the section entitled "Family History of Type 1 Diabetes" on the subject's Screening Form. The DCC uses this information from this section of the Screening Form to tabulate the total numbers of FDRs that have been screened and enrolled in the study; so it is important that the clinical center is updating this form with the new information. Once the clinical center has made the change and saved the Screening Form an automatic email is sent to the DCC which contains the information related to the change. The DCC then contacts the corresponding screening lab about this change.

NOTE: If a first degree relative of the TEDDY child develops Latent autoimmune diabetes of adults (LADA), then the site should update the Screening Form with the information that the child now has a first degree relative with Type 1 Diabetes in addition to recording the diagnosis on the Update form for Family History Questionnaire.

Infants are excluded from screening if they:

- Have an illness or birth defect that precludes long-term follow-up or involves use of treatment that may alter the natural history of diabetes (e.g. steroids or insulin).

5.3 Screening Procedures

Screening activities across all centers include the following elements with each described below for each Clinical Center and in detail in Appendix A1-6. Relevant forms and documents to each step are also available in the Appendix detailing the procedures at each clinical center.

1) Obtaining Informed Consent and, in the US HIPAA authorization (if required by the sites local IRB)
2) Screening process, providing materials to parents and answering questions.
3) Collection, Processing, and Shipment of the blood sample for HLA determination.
4) Registering participants with the DCC

5.3.1 Obtaining Informed Consent (all clinical centers).

A signed informed consent will be obtained for every study participant prior to the collection and processing of blood samples for HLA screening. The screening location and method used to obtain the informed consents will vary by study site, such as face-to-face, phone, or mail (see Table 5.3 for a summary).

In June 2009 the EEC approved the following wording to be added to all US sites' Screening Informed Consents:

> "The Genetic Information Nondiscrimination Act (GINA) is a new U.S. federal law designed to protect people from having their genetic information used in decisions about employment and health insurance. It prevents employers from using a person's genetic information to decide about hiring, firing, job placement, or promotions. Also, health plans and insurers must not deny coverage or charge higher premiums to a healthy person, based solely on that person's genetic risk of getting a disease in the future. GINA is designed to protect people, including children, who undergo genetic screening tests like those in TEDDY. It also lowers the risk of asking your health care provider to place TEDDY results in your child's medical record, where it could help in quicker and more accurate diagnosis if the disease does appear. For more information about GINA, please ask a TEDDY staff member."

Since screening will be done in many different institutions within one Clinical Center and these institutions may have informed consent language requirements, formats, and review processes there will likely be several variations of the basic informed consent document used in each clinical center. Model Informed Consent language is provided in Appendix B. Table 5.3 summarizes the types of screening locations and methods of obtaining informed consent at each clinical site. Site specific Screening Informed Consents are provided in Appendix C1-6.

Table 5.3: Summary of Screening Locations and Methods of obtaining informed consent by site

Clinical Center	Screening locations	Method of obtaining informed consent
Colorado	1. Hospitals – post delivery 2. Clinics/physician offices – pre delivery	Face-to-face Face-to-face or telephone
Finland	Maternity Clinics in three cities	Face-to-face
Georgia/Florida	1. Hospitals – pre and post delivery 2. Clinics/physician offices – pre and post delivery	Face-to-face Face-to-face or telephone
Germany	1. Hospitals – pre delivery 2. Clinics/physician offices – pre delivery	Face-to-face Face-to-face or telephone
Sweden	Maternity Clinics in five cities	Face-to -face
Washington	1. Hospitals – post delivery 2. Clinics/physician offices – pre delivery	Face-to-face Face-to-face

5.3.2 HIPAA Authorization (US Centers only)

Some US sites will require every participant agreeing to screening to sign a HIPAA authorization A form that meets the requirements of the institutions that are involved (university, hospital, clinic). It is the responsibility of each center to be attentive to and meet the HIPAA compliance and assurance procedures as required by the sites local IRB.

5.3.3 Screening process, providing materials to parents and answering questions.

The screening process varies between the six Clinical Centers (Table 5.4). Common to all is that FDR participants are recruited from families of diabetic children through registries, diabetes clinics, obstetric departments, pediatricians, general population screening or by advertising.

Table 5.4. Summary of screening process, providing materials to parents and answering questions.

FIRST DEGREE RELATIVES (FDR)

Clinical Center	Screening process	Providing materials	Answering questions
Colorado	Predelivery and Post-delivery invitation	Predelivery and Post-delivery visit	Predelivery and Post-delivery visit
Finland	Delivery invitation	Delivery visit	Delivery visit
Georgia/Florida	Predelivery and Post-delivery invitation	Predelivery and Post-delivery visit	Predelivery and Post-delivery visit
Germany	Predelivery invitation	Mail or Predelivery visit	Telephone
Sweden	Predelivery invitation	Predelivery at Maternity Clinics	Predelivery at Maternity Clinics
Washington	Postdelivery	Predelivery visit and	Predelivery visit,

	invitation	Postdelivery	Postdelivery and/or Telephone

GENERAL POPULATION

Clinical Center	**Screening process**	**Providing materials**	**Answering questions**
Colorado	Postdelivery invitation	Predelivery packet and Postdelivery visit	Postdelivery visit
Finland	Delivery invitation	Delivery visit	Delivery visit
Georgia/Florida	Predelivery and postdelivery invitation	Predelivery and postdelivery visit	Predelivery and postdelivery visit
Germany	Predelivery invitation	Predelivery visit	Predelivery visit or Telephone
Sweden	Predelivery invitation	Predelivery at Maternity Clinics	Predelivery at Maternity Clinics
Washington	Postdelivery invitation	Predelivery visit and Postdelivery	Predelivery visit, Postdelivery and/or Telephone

As part of the informed consent process and completion of the screening form several elements will be discussed to participants including: the screening phase of TEDDY, the potential for eligibility for the follow-up study, answers to questions about the study, diabetes, genetic screening, why we need particular information, and what to expect regarding when and how they will be notified of the results. It is important that all staff involved in conducting these interviews/conversations be well trained and comfortable with these elements and that we are giving consistent messages across sites. Study-wide and site specific materials are (or will be) available that are intended to document best practice guidelines for screening staff and form the basis for information that is provided for participants such as brochures.

5.3.3.1. Administration of the Screening Form

The Model Infant Screening Form (Appendix D) shows the required information and question wording for those elements that are needed by all sites. This form records selected demographic characteristics for the study participant (newborn and parent's), needed health information for determining eligibility into each cohort, contact information, HLA sample information and process information (e.g. visit location code, record of informed consent) and other study specific data across study sites. The DCC will use this information together with the HLA screening result to track screened subjects and determine who is eligible for enrollment into the follow-up study for each cohort (general population, FDR, pregnancy). Subject contact information will be gathered and held locally. The data elements that are required by all sites and their description is provided in Table 5.5 below. The required fields on the screening form will be transmitted to the DCC via the online screening registration form.

Each site may choose to add data fields to meet site specific needs related to their screening procedures. However, the tailored form must retain the basic elements of the standardized version. Details of these site specific forms are found in the appendices.

Table 5.5: MODEL SCREENING FORM: Data Description

Field name	Requirements: RS=Required to save form RC=Required to make form complete (in addition to all fields required to save from) N=Not Required P=Provided	Field Definition and Administration Rules:
Date of screening	RS	This field is defined by each individual TEDDY site: **Atlanta, Georgia** = Date on which subject's parent(s) consented to TEDDY screening. **Augusta, Georgia** = Date on which subject's parent(s) consented to TEDDY screening. **Colorado** = Date on which blood sample collected from subject through heel stick or cord blood collection. **Gainesville, Florida** = Date on which subject's parent(s) consented to TEDDY screening. **New York** = Date on which blood sample collected from subject through heel stick or cord blood collection. **Pennsylvania** = Date on which subject's parent(s) consented to TEDDY screening. **Washington** = Date on which subject's parent(s) consented to TEDDY screening. **Germany** = Date on which blood sample collected from subject through heel stick or cord blood collection. **Finland** = Date on which the online screening form was completed. **Sweden** = Date on which the screening sample is received and registered at the laboratory. Format: dd mmm yyyy (day, month, year) Drop-down lists for Month and Year.
Child's date of birth	RS	Date on which child was born.

		Format: dd mmm yyyy (day, month, year) Drop-down lists for Month and Year.
Local Code	RS	Local Clinical Center code assigned to subject. Format varies for each site.
Clinical Center	P	Name of TEDDY Clinical Center for which child's data is being entered. Automatically provided based upon person entering data.
TEDDY Staff Code (of Interviewer)	RS	TEDDY staff code of person who completed the child's screening form (interviewed parents).
Visit Location code	RS	Location where subject was screened at. Drop-down list based upon TEDDY Clinical Center field.
Subject Id	P	Subject TEDDY Id number assigned by DCC at time form is saved. Data not entered by TEDDY Clinical Center. Format: 6-digit numerical code
Has the child's parent(s) or legal guardian(s) given signed informed consent for the child to be screened?	RS	"YES" or "NO" must be selected. If "NO", subject cannot be entered into database. Prompt that arises with "No": **If the parent/legal guardian does not give consent, you are not able to register subject**
Sex	RC	Sex of subject: "Male" or "Female".
Singleton, Twin, Triplet or Other	N	Birth status: Singleton = Mother gave birth to one child Twin = Mother gave birth to 2 children Triplet = Mother gave birth to 3 children Other = Mother gave birth to > 3 children
Race (check all that apply) Suggested question wording:	RC	Race of subject as reported by subject's parent(s). More than one option may be selected. If not known, select "Unknown or not reported". Administration: This should be asked in a standardized manner, interviewer observation is not sufficient.
Hispanic Ethnicity Suggested question wording:	RC	Ethnicity of subject as reported by subject's parent(s). If not known, select "Unknown or not reported". Administration: This should be asked in a standardized manner, interviewer observation is not sufficient.
Mother's Date of Birth	RC	Date of birth for subject's mother. Leave blank if unknown or not provided. Format: dd mmm yyyy (day, month, year)

		Drop-down lists for Month and Year.
Father's Date of Birth	N	Date of birth for subject's father. Leave blank if unavailable. Format: dd mmm yyyy (day, month, year) Drop-down lists for Month and Year.
Family History of Type 1 Diabetes	RS	Identify if subject has first degree relative with Type 1 Diabetes. If "No" or "Unknown, relative field does not appear. If "YES", relative field appears and must be completed. Select all relatives with Type 1 Diabetes. NOTE: This field is used to separate General Population and First Degree Relative subjects. **Full Siblings only are recorded**
Study History	RC	Used to link family members participating in TEDDY.
○ Does this family have another child already enrolled in this study? *	RC	Select "Yes" if another family member is TEDDY Follow-Up Study subject.
○ If yes, please provide child's Local Code.	RC	If family member in TEDDY, use Local Clinical Center database to get child's Local Code.
○ Was the mother involved in the pregnancy study?	RC	Applies to Local Clinical Centers collecting samples from pregnant moms. Select "Yes" if mother of subject participated in TEDDY pregnancy study.
○ If yes, please provide Mother's Local Code.	RC	If mother was in TEDDY pregnancy study, use Local Clinical Center database to get mother's Local Code.
HLA Sample Information	RS	Section required to track samples as processed.
○ Sample draw date	RS	Date on which blood sample collected from subject through heel stick or cord blood collection.
○ HLA screening sample number	RS	Local Clinical Center code assigned to subject's HLA screening sample. Format varies for each site.

*If a family has another one of its children screened for TEDDY (one of its children is already enrolled in TEDDY) it is only necessary to mark 'yes' to 'Does this family have another child already enrolled in this study?' on the child's screening form that is currently being screened. Do not go back and change the answer to 'yes' for this question on the screening form for the other sibling who is already enrolled in TEDDY.

5.3.4 Frequently Asked Questions (FAQs)

Purpose: The FAQs are intended primarily for, but are not limited to, two uses (a) as a training document for screening and recruitment staff, and (b) as a source for developing materials for study participants (e.g. brochures, quick reference FAQ sheet, etc). It is also intended as a document to be updated as needed with input from all clinical sites about questions and agreed upon answers that are asked about screening and about the TEDDY study. The FAQ file has questions and wording of answers identified and reviewed by all study sites.

Source and maintenance of FAQs:

- *Primary Contact*: The Study Coordinator Committee and the DCC will be responsible for compiling, updating, and maintaining the FAQ document. The FAQ document (Appendix E) will be available for download from the TEDDY website.
- *Document updates*: As new FAQs undoubtedly emerge with the implementation of TEDDY, each site will be responsible for *FAQ Draft*: An initial master FAQ document was complied in Spring 2004 based on previous experience at some sites and reviewed by the psychosocial committee. This draft is available to all sites to assist initial start up activities and staff training.
- Recording new questions that are routinely coming up during screening as well as recording suggested changes to existing questions. Each site will determine how best to include input from all staff members involved with screening. The Study Coordinators Committee on a regular basis will review these suggestions and issues. Suggested changes will be reviewed with the steering committee Review and the document updated.

5.3.5 Brochures and materials left with consenting subjects.

The TEDDY screening brochure is left with the consenting subject along with the consent form and a signed copy of the consent and in the US a signed copy of the HIPAA form.

5.4 Collection, Processing, and Shipment of the blood sample for HLA determination.

Genotype screening will be performed using either a dried blood spots (DBS) or a small volume whole blood lysate (WBL) specimen. The method of collecting blood samples will vary by study site and are detailed in Appendix A1-6 for each Clinical Center.

Table 5.6. Summary of collection, processing, and shipment.

Clinical Center	Collection	Processing	Shipment
Colorado	Cord blood & heel stick	0.5 ml WBL	Weekly mail
Finland	Cord blood	DBS	Daily by mail
Georgia/Florida	Cord blood &	DBS	Weekly/Daily by

	heel stick		mail
Germany	Cord blood & Heel stick or Venous blood	DBS	Weekly by mail
Sweden	Cord blood	DBS	Daily by mail
Washington	Heel stick	DBS	At one month

WBL is Whole Blood Lysate, DBS is Dried Blood Spot and TRF is Time Resolved Fluorescence

The blood samples are collected at the time of delivery from the umbilical cord or obtained postdelivery as a heel stick. Sampling is done by obstetricians or mid wife who are instructed in the procedures by TEDDY personnel. Written site-specific TEDDY instructions should be made available to be left in the delivery room.

General WBL procedure: Cord blood is collected in 7 ml or 15 ml EDTA (lavender top) labeled test tubes which are capped and turned four times to prevent the blood from clotting. The tube is collected every day from the maternity ward to the TEDDY clinic for processing as described in the site specific description in the Appendix. Briefly, 0.5 ml blood is removed to a 1.5 ml test tube labeled with the local ID number, kept at -20 C until mailed on dry ice to the HLA typing laboratory. Samples are mailed in batches every Monday morning.

General DBS procedure: Delivery room personnel (obstetrician or midwife) will drop cord blood directly from the cord or from a separated cord blood collecting EDTA (lavender) top tube. The filter paper has 3-6 printed rings on which the blood is dropped. The filter papers are labeled and may have a remittance attached. The obstetrician or midwife fills out the remittance. The blood on the filter paper is allowed to dry on the bench for 30-60 min before being collected and either picked-up by TEDDY personnel on a daily basis or sent by mail to the TEDDY laboratory which is often identical to the HLA typing laboratory of the respective Clinical Center (see Table 5.7 and Appendix A1-6).

Table 5.7: Summary of HLA typing laboratories

	Laboratory location and head	**HLA typing method**
Colorado	Roche Henry Erlich	Reverse Lineblot
Finland	University of Turku, Turku Jorma Ilonen	TRF hybridization with sequence specific probes
Georgia/Florida	Medical College of Georgia, Augusta , Georgia Jin-Xiong She	Denaturing gradient gel electrophoresis & Luminex beads with sequence-specific probes
Germany	University of Turku, Turku Jorma Ilonen	TRF hybridization with sequence specific probes
Sweden	University Hospital MAS, Malmö Anita Nilsson	TRF hybridization with sequence specific probes
Washington	PNRI, Seattle , WA William Hagopian	TRF hybridization with sequence specific probes and direct sequencing

Additional processing and shipment procedures are center specific and are detailed in each center's manual of operations in the Appendix A1-6. Samples are tracked through the process of enrolling screening subjects into the local and DCC databases where Subject IDs are assigned and samples are then labeled with this id and shipped with a specimen tracking form generated from the TEDDY website to the local laboratories performing the initial HLA genotyping.

5.5 Registering new participants with the DCC

5.5.1 Online Registration

1) Complete clinical center specific screening form.
2) Go to TEDDY website: www.TEDDYstudy.org
3) Click on "Register Newborn" under the Data Management heading on the left navigational bar.
4) Complete online screening form.
5) Required fields to save the form include (these fields are marked with a red "*"):
    - Child's date of birth
    - Local Code
    - Clinical Center
    - Testing Location
    - Family History of T1DM
    - HLA Sample Draw Date
    - It is also required that the child's parents or legal guardians have signed the screening informed consent. This can be indicated on the online screening form.
6) Required fields to make the form complete (these fields are marked with a blue "*" and are in addition to the fields that are required to save the form):
    - Sex
    - Race
    - Ethnicity
    - Mother's date of birth
    - Study History
7) Once the form is complete click "Save", or "Save and Print" if you want a print out of the form.

A unique Subject ID will then be assigned to this individual and they will be registered in the study. This Subject ID number will appear at the top of the screening form next to the Local Code.

5.5.2 What to do if you submit a screening form for a subject by mistake or you submit a screening form for a subject and no HLA screening sample is able to be collected

If you mistakenly register a subject (submit two screening forms for one subject, submit a screening form for a subject that does not exist) contact the DCC and explain the situation. Based upon the provided information the DCC will then change the status of the subject from "Registered" to "Registered in Error".

If you submit a screening form for a subject and then no HLA screening sample is able to be collected or the HLA screening sample is lost, contact the DCC and explain the situation. Based upon the provided information the DCC will then change the status of the subject from "Registered" to "Not Screened".

5.5.3 Instructions for using the Withdrawal of Screening Consent Form

1) The Withdrawal of Screening Consent form is only to be used for those participants who withdraw consent for the screening portion of the study, not the follow up. For those refusing consent of the follow up portion of the study, please complete the Enrollment Form.
2) Login to the TEDDY Members website.
3) Click on 'Enter/Edit/View' under the section heading 'Data Management' on the left navigation menu.
4) Search for the desired subject by entering one of the following: 1) Local Code and Subject ID 2) Local Code and Date of Birth 3) Date of Birth Range 4) Clinical Center and Subject ID 5) Clinical Center and Local Code or 6) Clinical Center and/or Visit Location Code.
5) Under 'Search Results' Click on the subject's Local Code to view that subject's Participant Details page. This page gives a list of all activities (forms, samples, etc.) done for a particular subject.
6) Select 'Withdrawal of Screening Consent' from the drop down list under 'Additional Study Forms' heading and click 'Select Form'.
7) Enter the TEDDY Staff Code, Date of Withdrawal, and explanation of why the participant has chosen to withdraw consent.
8) Click 'Save' or 'Save & Print' to save the Withdrawal of Screening Consent form, then 'Close' to close the form.
9) Once you have saved the form, the DCC will review the request to have the subject withdrawn. Once the DCC has either approved or denied the withdrawal request, you will receive an email notification. If the request is approved, the status of the participant will change to 'Withdrawn Screening Consent'.

5.5.4 How to change a subject's First Degree Relative status after screening form has been submitted to the DCC

If you submit a screening form to the DCC and then obtain information that changes the subject's First Degree Relative status you should update the screening form with the new information and re-save the form. The DCC will receive an automatic email regarding the change and will notify the corresponding HLA screening lab about the change in FDR status, if necessary.

NOTE: If a first degree relative of the TEDDY child develops Latent autoimmune diabetes of adults (LADA), then the site should update the Screening Form with the information that the child now has a first degree relative with Type 1 Diabetes

in addition to recording the diagnosis on the Update form for Family History Questionnaire.

5.6 Using the Sample Shipment System for HLA screening samples

1) Logon to the TEDDY website, http://teddy.epi.usf.edu/
2) Go to the "Sample Shipment System" located on the left navigational toolbar under "Data Management".
3) Enter the date of shipment.
4) Choose the "HLA Screening Lab" option under "Select where samples will be shipped to".
5) For samples being shipped to the "HLA Screening Lab" there are two ways to indicate shipment of the sample in the system:
    a. Upload one .CSV file with all subject IDs included:
        i. Enter the heading title "SUBJECTID" in cell A1
        ii. Enter the subject ID associated with each HLA screening sample in column A beginning with cell A2 of the .CSV spreadsheet file.
        iii. Save the file using the following naming convention: SLYYMMMDDn.csv
            1. The "SL" stands for Screening Lab. It lets our computer system know what data to expect in the file.
            2. The "YYMMMDD" is the date the file is being uploaded to the TEDDY website. ***NOTE: Year is first in the name in order for the DCC to sort the files by type of file and year.**
            3. The "n" is a unique number starting at 1 each day and is used in cases where a site may be uploading more than one file on a given day. For example, if two files are uploaded on 9 August 2007, please name them : SL07AUG091.csv and SL07AUG092.csv
        iv. Click on the "Browse" button to locate the file you want to upload to the TEDDY website. Click on the desired file, and then click open. The file location and name should appear in the field next to the "Browse" button.
        v. Click the "Upload" button.
        vi. Once the file has been successfully uploaded you will see the information pertaining to each Subject ID submitted in the file populated in the table below the upload function.
    b. Enter each subject ID individually
        i. Type in the subject ID associated with the HLA screening sample in the provided field and then press the 'Tab' key.
        ii. Repeat these steps until you have entered the subject ID associated with each sample you will be shipping to the HLA screening lab.

6) The Subject ID, Local Code, Clinical Center, Test Name, Vial barcode number, Visit Location Code, whether the sample is associated with a First Degree Relative or not and Date of Draw will appear for all the samples.
7) Enter the tracking number and courier service for that shipment and any comments you would like to notify the lab about.
8) Click on "Print and Email Shipping List". A dialog box will open that asks "Are you sure you want to print and email the shipment list?" Press 'OK' if you do and 'Cancel' if you don't.
9) Once 'OK' has been clicked an Excel file will be created that will contain information pertaining to each sample (Vial Barcode Number, Subject ID, etc).
10) Save this file for your records; an email containing this file will automatically be sent to the DCC and to the screening lab.
11) Print out a copy of this list to be shipped with the samples.

5.7 Screening Staff Training

Training of recruiters and other staff for screening procedures will vary across clinical sites, countries, private or public institutions, as well as across the cohorts being screened. Recruiters must fulfill the mandatory training requirements set forth by the institutions where they will be working or affiliated. Across all clinical sites, however, a minimum level of certification and training should be met by all recruiters and staff who will be engaged with study participants and/or handling blood samples for the screening phase of the study.

Basic requirements for all screening recruiters should include:

- IRB and HIPAA certifications [U.S. sites]
- Blood borne pathogens training
- Phlebotomy (if drawing blood from participants)
- Standardized TEDDY screening orientation and training (see below)

Standardized TEDDY screening orientation and training

Each clinical site should include these same basic features as part of training and orientation for recruiters.

- Provide overview of TEDDY Study (international and site specific).
- Review and explanation of TEDDY MOO. Emphasis placed on site specific screening process MOO.
- Detailed review of data collection forms and description of reason/need for each field.
- Role-play participant interview and informed consent.
- Conduct observational and quality control on-the-job training (recruiter observes how interview should be conducted and then supervisor observes recruiter conduct interview multiple times to assess and ensure master of the protocol).
- Demonstrate and have recruiter practice every step of the blood collection process until mastered. Recruiter must successfully complete 100% of identified key cord blood collection steps 3 times.
- Give tour of clinic, lab, hospital, etc and introduce recruiter to staff.
- Provide informational articles on diabetes and study's FAQs.
- Recommended:

- Certify/observe at least 3 screening encounters semiannually with individual recruiter(s). Debrief.
- Quarterly meetings with recruiters to review emerging issues, protocol questions, quality control debriefs.

Section 5 – Appendix

A. Site Specific Screening Procedures
1. Colorado
2. Finland
3. Germany
4. Georgia/Florida
5. Sweden
6. Washington

B. Model Screening Informed Consent

C. Site Specific Screening Informed Consents
1. Colorado
2. Finland
3. Germany
4. Georgia/Florida
5. Sweden
6. Washington

D. Model Infant Screening Form

E. Model Screening Frequently Asked Questions

A1. Site Specific Screening Procedures: Colorado

Site specific training

COLORADO

Overall training procedures for recruiters at the Colorado site are similar for the hospital and clinic sites. All recruiters are given a standardized TEDDY Study training session at the beginning of their employment (described below). Each hospital has different procedures in place as to how a recruiter is hired. They are either University employees, hospital employees or both in certain cases. Therefore, recruiters will also complete additional training sessions based on the requirements of the institution in which they will be working.

Colorado began TEDDY screening September 1, 2004 at one hospital and one clinic site in Denver. Seven hospitals have been added as screening sites since then and this section of the MOO lists the procedures and trainings as they differ between sites. As new hospitals and clinics are added as screening locations, their training requirements will be updated in this section.

Colorado Training for Screening Recruiter Staff

All recruiters (hospital and clinic) will complete a standardized TEDDY Study training session. The training sessions are broken down into two main parts: a general training session (Part I) and a didactic on-site training (Part II). The trainings are conducted when new employees are hired, either in a group or as individuals.

Part I: General training session

This first session is an overall orientation intended to review the major features of the study, the position, and the job procedures. This session lasts about 4-5 hours and is scheduled for either a single day or split between two consecutive days. The session is usually conducted by the Screening Coordinator or Assistant Screening Coordinator, but can be conducted by another trained TEDDY staff member.

Notebook: Each recruiter is given a notebook of materials.

- Checklist for new recruiters
- Agenda for training session
- TEDDY Study Information (Screening summary sheet, Protocol Summary)
- DAISY Study Information
- TEDDY Colorado site-specific Manual of Operations
- TEDDY forms (Infant Screening Form, Informed Consent, HIPAA,
- Interview Script
- FAQs
- Policies & Guidelines
- Staff contact roster
- Shift Schedules/Calendars
- Diabetes Articles

Training Agenda: Using the notebook as a guide, the training session will thoroughly cover several key areas. New recruiters will be encouraged to ask questions and are expected to actively participate.

- Overview of study structure with emphasis on the recruiter's role on project
- Review of manual of operations (MOO)
- Explanation of forms and consent process
- Role playing of interview process
- Review of FAQs and discussion about the types of questions, issues, and problems they will encounter
- Review study policies and expectations
- Tour of TEDDY facilities at UCHSC and introduction of staff

Near the end of the training session, the Screening Coordinator will assess if the recruiter comprehends the information and can satisfactorily perform patient interviews. If so, they will be incorporated into the hospital or clinic's screening schedule, with the first two days serving as didactic on-site training.

Part II: Didactic on-site training (multiple days)
Day One: The first day of didactic training is held at the site in which the recruiter will be working and lasts the length of a typical shift (about 4-5 hours). This day is primarily observational for the recruiter, with the Screening Coordinator (or other TEDDY staff member) demonstrating the screening procedures. The first hour involves reviewing the materials from the general training session and answering all the recruiter's questions. The patient interview is practiced again. The recruiter is also probed with scenarios to identify potential areas that need clarification.

After the materials are reviewed, the recruiter will observe the screening coordinator and go step-by-step through all the screening procedures for the day. The coordinator will explain every step in detail and are encouraged to ask questions throughout the process:

1. Demonstrate where to obtain required paperwork and how to organize paperwork for the days work. [Hospital and clinic]
2. Demonstrate daily cord blood assessment and initial data collection procedures. [Hospital only]
3. Demonstrate patient interview procedures with actual patients multiple times as recruiter observes. Discuss after each interview issues and questions that come up during the encounter. [Hospital and clinic]
4. Give recruiter the opportunity to conduct a patient interview while coordinator observes. Step in and prompt if necessary. Discuss encounter with recruiter after completion. Provide suggestions for improvement, point out important points that were forgotten, and offer compliments as appropriate. Continue steps 3 and 4 until recruiter has a good mastery of procedures.

Day Two: The second day of training is planned with the recruiter as the active member of the dyad with the Screening Coordinator, or other trained TEDDY staff member, as the observational member. The goal is for the recruiter to practice all the steps and procedures from start to finish while using the trainer as back-up support. The coordinator or other TEDDY employee observes the recruiter during all procedures and offers pointers, guidance, and positive reinforcement. Consideration is made to make sure the recruiter has mastered the procedures by

the end of the day. If not, another didactic training session is scheduled. The recruiter may also request another training session to ease her/his comfort level.

Follow-up Support: The Screening Coordinator and Assistant Coordinator remain available via phone and email for the recruiters after formal training has been completed. Recruiters are encouraged to contact the coordinator with questions or for clarification. Experience has shown us that the more support you can provide recruiters in the first two months in their duties, the more self-sufficient and confident they will be. Support can take many forms such as being readily available to answer questions, identify and implementing solutions to problems they are having at the screening site, to general words of encouragement and appreciation. Feedback from the recruiters to the coordinators is also encouraged. Once the recruiter has been working on their own for a few weeks, the Coordinators will shadow them again, as a measure of follow-up quality assurance and to answer any questions that may have come about.

ADDITIONAL TRAINING REQUIRED FOR RECRUITERS

Hospital Recruiters

Exempla Hospitals

- Attend Hospital orientation
  - Occupational safety training (biohazard materials/blood borne pathogens, emergency procedures, signs, exit location, etc).
  - HIPAA training – verbal presentation and self-study booklet with hand in test.

HealthONE Hospitals

- Attend Hospital Orientation
  - Occupational safety training
  - HIPAA training – verbal presentation and self-study booklet with test.
- Employee Health Pre-Employment screen completed

Centura Hospitals

- Attend Hospital Orientation
  - Occupational safety and blood borne pathogens training
  - HIPAA training – verbal presentation and self-study booklet and hand in test.

University of Colorado at Denver and Health Sciences Center Employees

- HIPAA on-line training course completed within one week of general training session
- COMIRB CITI Basic course (Protection of Human Subjects)- online course completed within one week of general training session
- Blood Borne Pathogens on-line course completed within one week of general training session

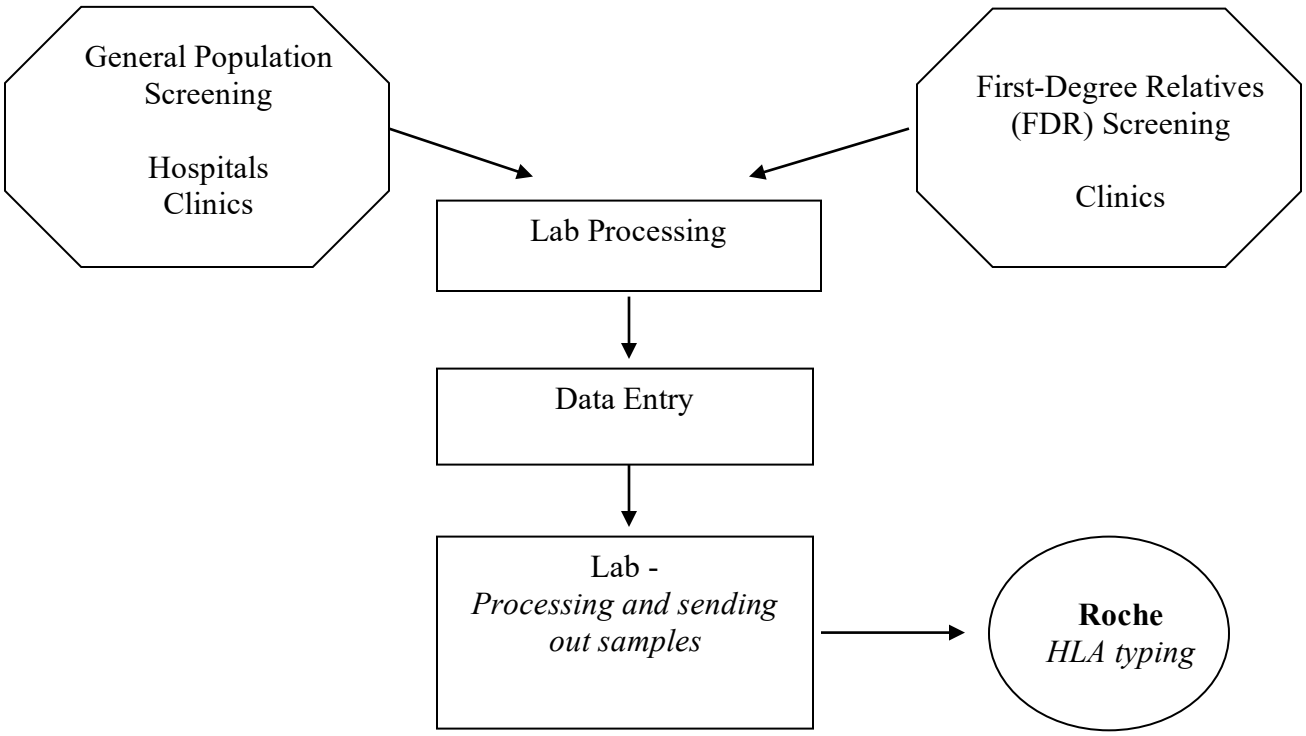
Most recruiters will fall under two of these categories and will complete both the University requirements and Hospital requirements. All recruiters will meet the hospital requirements for training.

Clinic Recruiters

Barbara Davis Center (University of Colorado employees)

- HIPAA – On-line training course - completion required within 1 week of hire date.
- COMIRB CITI Basic course (Protection of Human Subjects) online course completed within one week of hire date.
- Blood borne pathogens course – required before handling blood samples.
- Phlebotomy training (or certification of previous completion).

Site specific implementation
COLORADO
Flow chart of Colorado screening process



GENERAL POPULATION SCREENING PROCEDURES - HOSPITALS

Cord Blood Samples

Cord blood collection at delivery

Cord blood samples are routinely collected in delivery at local hospitals for their own purposes (generally red-top tubes). All obstetricians, family practice physicians and labor and delivery staff at participating hospitals have been informed about the TEDDY Study and the necessity of collecting a cord blood sample in a purple top tube for every baby delivered. The purple top tube contains EDTA, a chemical that prevents the blood from clotting, thus allowing the study to keep the sample on hand for a few days before a family gives their consent. The physicians and L&D staff are given the following instructions:

> "Cord blood samples should be collected in the 5mL lavender-top tubes. These tubes are sterile and will be put in the delivery set-up by the nurses or scrub-techs. Please obtain the routine red-top tube sample first, as well as any samples required for families banking cord blood, and then fill the lavender-top tube. Before you put the lavender-top down, mix the blood by gently inverting the tube 8-10 times. This is important because it keeps the blood from clotting. This tube will be labeled in the same manner as the red-top tube and will be stored in the scrub room until collection and processing by our study recruiters who are also responsible for obtaining informed consent from the mothers."

Because there is only one lavender-top tube in the kit routinely used by the hospital, the nurses and doctors require additional tubes for twins, triplets, etc. TEDDY supplies the hospital with these additional lavender-top tubes. For those hospitals that do not already have a lavender-top tube in their delivery pack, TEDDY can provide these tubes if needed. A TEDDY recruiter or staff person will bring a supply of lavender-top tubes to the appropriate Labor and Delivery contact person as needed.

Samples for Recruiters

After the deliveries, the cord blood samples (red-top and lavender-top tubes) are labeled. The red-top tube is sent to the hospital's lab for processing. The purple-top tube is set aside in the designated area of the soiled utility room for the study. The blood sample is considered property of the hospital until it leaves the hospital and goes to the TEDDY lab. Therefore, if the recruiter is approached by hospital staff (pre or post consent) asking for the blood sample, the sample must be given to them. The process for which the samples are made available to the recruiters varies by hospital.

Exempla St. Joseph's Hospital

Cord blood samples are collected by the L&D scrub techs in a back utility area for temporary holding. At the end of the scrub techs shift (7am and 7pm) the collected cord samples are brought to the Dirty Utility Room across the hall from the nurse's station in L&D. These samples are stored in biohazard bags, placed in the plastic bin labeled "New Samples" and left for the TEDDY recruiters. The latest blood delivery is expected by 7:30 a.m. each morning, at the beginning of the recruiter's shift. Pending samples leftover from the previous day will be in a bin labeled "pending" and the recruiter will approach these patients along with those from the current day. There is no code for access to this room.

Exempla Lutheran Medical Center

Cord blood samples are placed in a red biohazard bin in the Dirty Utility Room by the L&D nurse's station immediately after baby's delivery. Samples are placed in individual plastic biohazard bags within the red biohazard bin. Pending samples will be in a clear bin marked "pending". There is no code for access to this room.

Exempla Good Samaritan Medical Center
Cord blood samples are collected by L&D staff and brought to the soiled utility room near the nurse's station on that unit immediately after delivery. New samples are placed in a tube rack on the counter and "pending" samples are kept in a clear bin labeled pending on the shelf labeled "reserved for research." The access code for this room is 9998#.

HealthONE Rose Medical Center
Cord blood samples are collected by L&D staff and stored immediately after delivery in the soiled utility room across from the Labor and Delivery nurse's station. All new samples will be placed in the clear bin labeled "New Samples" and all pending samples from the previous day will be in a clear bin labeled "pending." The code for access to this room is 123*.

HealthONE Swedish Medical Center
Cord bloods samples are collected by L&D staff and stored in the soiled utility room behind the nurse's station immediately after delivery. New samples will be stored in clear biohazard bags and placed in a beige holding bin. Pending samples will be stored in a clear bin labeled "pending." The code for access to this room is 3-4.

HealthONE Sky Ridge Medical Center
Cord Blood samples are collected by L&D staff and stored immediately after delivery in the soiled utility room next to the nurse's station. The samples will be placed in a cabinet labeled with a sign for TEDDY Study Samples and individual samples will be placed in a clear bin labeled "New Samples." Pending samples will be stored in a clear bin labeled "pending." The code for access to this room is 1010*.

HealthONE Medical Center of Aurora
Cord Blood samples are collected by L&D staff and stored immediately after delivery in the soiled utility room on the Labor and Delivery unit. Samples are stored in a locked cabinet with code 1-3. New samples will be in biohazard bags and placed in a clear bin labeled "New Samples." Pending samples will be stored in a clear bin labeled "pending." The code for access to the soiled utility room is 1501.

Centura Avista Adventist
Cord blood samples are collected by L&D staff and stored immediately after delivery in the soiled utility room on the Labor and Delivery unit.

Screening Recruitment
Hospital screening is divided into 3 phases: pre-interview, interview, and post-interview.

PRE-INTERVIEW PROCEDURE
A TEDDY recruiter will arrive at the hospital for the daily shift (generally starting between 8:00-8:30 depending on the hospital and working until 11:30 a.m.) seven days a week. The recruiter follows a series of steps during the pre-interview process to prepare for the Interview process with the patients.

1. Go to the recruiter's supply space to gather all the necessary forms for the shift and to review any notes left by the previous day's Recruiter. Collect the following materials and put them in the black tote bag provided by the study:
    a. Informed Consent Packets
    b. File Folders (labeled: Tracking Form, Pending, Consented, Ineligible, Refused, and New)
    c. TEDDY brochures
    d. Clip Board, stapler, paper clips, pens, etc

It is helpful to have 1-2 weeks worth of individual packets of the required forms made up ahead of time. The packets include collated copies the informed consent and for Exempla Hospitals the HIPAA form.

2. Go to the Utility Room in Labor & Delivery where cord blood samples are located. At some hospitals in order to verify that all cord bloods are present, the recruiter may ask the current shift of scrub techs to double check to make sure all cord blood samples have been brought to the soiled utility room. After putting on a pair of gloves, the recruiter looks at the biohazard bags containing the cord blood samples and organizes the samples in the following way:
    a. Pending: Compare the samples in the bin marked "Pending" with the Infant Screening Forms in the Pending folder from the previous day. Make sure names match. Leave pending samples from previous day in the plastic bin and set aside. Set aside the forms.
    b. New Samples: The remaining samples (in unmarked bags and/or new sample bins) are the new bloods from the last 24 hours. Remove the samples from the biohazard bags and gently lay them on a towel or another flat biohazard bag. Organize the tubes into rows with the label facing upwards.

3. The recruiter then writes the following information for each of the new samples on the Infant Screening Form (from the label on the tube):
    - Mother's first, middle, and last names
    - Mother's date of birth (clearly indicate to the left of mom's DOB if she is 16 or 17 as reminder to obtain witness signature.)
    - Mother's hospital ID number
    - Type of birth: single, twin, or triplet
    - Whether mom is a Kaiser Permanente patient for St. Joe's patients only. Indicate by writing KP in upper left corner of form.

NOTE: *These initial patient data fields are collected at this point in the research process (instead of after families have agreed to consent) because the genetic screening is only available to babies for whom a cord blood sample is available. Approximately5- 10% of the time, cord blood samples are not available for each baby (e.g. blood was not collected due to maternal or newborn complications during delivery, not enough blood in umbilical code, broken test tube, or fetal demise). Basic patient identifiers are therefore collected only for the purpose of locating the parents of the eligible newborns in order to offer the free screening. Care is taken to ensure families for whom we do not have a cord blood sample are not approached.*

Problems with the samples are likely to be encountered as forms are being filled out. The following guidelines should be followed when these occur. If a problem arises that is not listed or the recruiter can not trouble shoot a solution with the L&D staff, the Screening Coordinator or Assistant Screening Coordinator should be called or paged.

GUIDELINES

Problems with blood samples

1. Carefully asses the problem(s).
2. If blood has spilled out of a test tube into the bag, the recruiter IS NOT to open the bag or attempt to fix the problem. Get a scrub tech to clean up the bag and to salvage the remaining samples by cleaning off the blood from the test tubes and making sure the labels are readable. Throw away the sample that was opened. If the spill has caused other

samples to become contaminated or makes a label illegible, all affected samples must be thrown away.
3. If a label is torn, but the identity on the label is still discernable have a scrub tech get a new label. If the identity can not be determined with 100% accuracy, throw away the blood sample.
4. If a sample does not have a label the samples must be discarded. This should be indicated on the tracking form as a sample that was collected but ineligible due to a missing label.
5. If you receive blood samples that have identical labels, but no other written notations, go get a scrub tech. Have the scrub tech determine whether the sample is from a multiple birth or whether they are duplicate samples from a single birth. If they are from a multiple birth, they must be thrown away, as instructed in the procedures for multiple births below (see #3). If it is from a single birth, throw one of the samples away and keep the other.
6. If mom is 15 years of age or younger the sample must be discarded.
7. See problems with multiple births samples below.
8. Contact the Screening Coordinator if the problem is not described above or if you do not know what to do.

Procedures for multiple births

1. Blood samples for twins or triplets must be clearly labeled as Baby A, Baby B, or Baby C. It is extremely important to make sure the correct baby identifier is tracked for these births at every step in the screening and consenting process.
2. Each baby must have its own separate Screening Interview Form and consent form filled out. The correct baby identifier (A, B, or C) must be clearly marked on each form.
3. If blood samples are not clearly marked (ie. Baby A, B, or C) on the tube the samples must be thrown away in the biohazard sharps container. Mark these on the Daily Tracking Form in the "Ineligible" column. Only samples for which you can discern the identity with 100% accuracy can be kept for consenting.
4. In some cases you may only be able to consent one or two babies from a set of multiples because the blood samples were not all available. If this is the case, make sure you clearly distinguish at every step of the process which baby (or babies) will be screened. To prevent confusion make sure you explain to the parents which baby/babies will be screened and why (e.g. a blood sample was only available for Baby A).

4. Once all the names are collected and any problems resolved, the recruiter places the new blood samples in the bin labeled "samples in progress." The pending samples will be kept in the bin labeled "pending."

   NOTE: *Recruiters must remember to remove their gloves and wash their hands thoroughly before leaving the utility room (≥ 20 seconds).*

5. Next the recruiter gathers the Infant Screening Forms for the pending and new bloods and takes them to the mother-baby unit (MBU). The recruiter will then locate the mother's names on the white census boards in the nurse's station to write down additional information on the Infant Screening Forms:

Fields to fill in	Where to write on form
Mother's room #	On top of form

Baby's DOB	In provided space on form
Baby's time of birth	Next to baby's DOB (if given)
Baby's sex	In provided space on form (if given)
Type of birth (vaginal or C-section)	In provided space on form
Whether baby is in NICU	Write NICU on top of form
Whether mother and baby are going home that day	Write "H" on top of form

The type of information listed on the census board, as well as how the information is indicated varies by hospital:

Exempla St. Joe's:

There are two MBU units on the 2nd floor. The white census board with information for all rooms is located in the nurse's station of the main unit. Rooms 201-224 are in this unit. Rooms 240-256 are on the unit between the main unit and L&D. Mom's are frequently also in rooms on the 3rd floor or 10th floor in very rare cases. If a patient is not listed on the board, check with the unit clerk as they may be on one of these floors. If so, check with the nurse's on the appropriate unit to see if it is ok to speak to these patients.

Write on Form:

- Mother's room number (write in upper left corner of form)
- Baby's date of birth
- Baby's time of birth (indicated next to baby's DOB)
- Baby's sex
- Type of birth (vaginal or C-section)
- Whether family is going home that day (noted as "H" on top of form)
- Whether baby is in the NICU
- Whether mom is a Kaiser patient (indicated as KP on top of form)

Definition of notations on white census board in mother/baby unit:

- Mom's name is listed by last name
- Baby's sex is color coded: All information will be written in one color. Girl= Purple, Boy= Orange
- Mom's room number is listed just to the left of her name. If only the name and room number is listed, not type or time of birth, they are still in L&D
- Baby's DOB written to the right of mom's name.
- Baby's time of birth written in military time. Indicate time of birth on the screening form if it was early on the same morning of screening.
- H= Written next to mom's room number indicates that the family is planning on going home that day. See these patients first.
- N=Means baby is in the NICU. Indicate on the screening form and check with mom's nurse to see if it is ok to approach this family.
- Red Dot means mom is relinquishing the baby. Ask mom's nurse if this is an open adoption. If so, follow policies for open adoption. If not dispose of sample and screening form at the end of the shift
- * Next to a name indicates name alert. There are two patients with this name so double check that you are seeing the right one

Exempla Lutheran:

There are three separate areas that make up the mom/baby unit on the 2nd floor. The white census board behind the nurse's station on the main unit has information for patients in all three areas.

Write on Form:

- Mom's room number
- Baby's DOB
- Type of birth (vaginal or C-section)
- Whether family is going home that day
- Whether baby is in special care nursery

Definition of notations on white census board in mom/baby unit:

- Mom's name is listed by last name
- Last name in parentheses (Smith) indicates mom will be moved to that room but she has not been transferred from L&D yet
- Baby's DOB written to the right of mom's name (if baby is born on the morning of screening double check the time to see if it is appropriate to see them as time of birth is not indicated)
- Type of delivery is color coated: Vaginal= all information written in purple/blue, C-section= all information written in red
- H= family is planning on going home that day, see these patients first
- SCN= baby is in Special Care Nursery, check with nurse to see if it is appropriate to see this family
- * Next to mom's name indicates name alert, there are two patients with this name so make sure you are seeing the right one
- Heart with a line crossed through it indicates fetal demise. DO NOT see this family

Exempla Good Sam:

There is one white census board located for all patients on the mom/baby unit on the 3rd floor. Rooms are numbered from 1-24

Write on Form:

- Mom's room number
- Baby's Date of Birth
- Baby's time of birth
- Type of birth (vaginal or C-section)
- Whether family is going home
- Whether baby is in the NICU

Definition of notations on white census board in MBU:

- Mom's name is listed by last name
- Baby's DOB listed to the right of mom's name
- Baby's time of birth indicated as the hour in which baby was born. If time of birth is listed as 04 that means baby was born sometime within the 0400 hour. Check with nurse for births after 04 to see if it is appropriate to see these mom's
- Type of delivery is color coded. Red= C-Section, Blue= Vaginal
- N= Baby in NICU, check with nurse before approaching this patient
- H= family planning on going home, see these patients first

HealthONE Rose:

The white census board is located in the nursery on the 3rd floor. The employee id badge should grant access to the nursery, if not there is a telephone to the left of the door of the nursery. Picking it up will ring the nurses and they will let the recruiter in. There are two separate areas on the mom/baby unit of the 3rd floor with patient rooms, suites on the 6th floor and a perinatal unit also on the 3rd floor. Rooms on the main unit are numbered 303-326 with an additional unit with rooms 330-342 near the nursery. For patients in the 6th floor suites, recruiters will have to ring the bell to be granted access and tell the nurse at the desk which patient they are there to see. If a patient is on the Perinatal unit (next to L&D) check with the nurse on that unit to see if that mom can be approached. After checking the white board in the nursery, recruiters will check the log book located at the main nurse's station to see the time mom was transferred from L&D.

Write on Form:

- Mom's room number
- Baby's DOB
- Baby's sex
- Type of birth (vaginal or C-section)
- Whether family is going home
- Whether baby is in Intensive Care Nursery
- Whether mom is in Perinatal Unit

Definition of notations on white census board in nursery

- Mom's name listed by last name
- Mom's name in parentheses (Smith) indicates that is room mom will be in, but she has not been transferred from L&D yet
- Baby's DOB written to the right of mom's name
- Baby's sex written in as boy or girl
- Type of birth is color coded, Red= C-section, Blue= Vaginal
- ICN= baby is in intensive care nursery, check with nurse before approaching these families
- PNU= mom is in Perinatal unit. Check with nurse on this unit to see if it is appropriate to speak to mom
- H= family is planning on going home that day, see these patients first

HealthONE Swedish

The white census board is located in the nurse's station of the mom/baby unit on the 5th floor. There are two main hallways with patient rooms numbered 5-133 through 5-155 and a smaller unit near the nurses station numbered 5-267 through5-274. There are also two rooms which are occasionally used as overflow, but more often for mom's needing special attention. These rooms are 275 & 276. If mom is in one of these rooms, the recruiter must be sure to check with the nurse first to see if it is appropriate to approach this family.

Write on Form:

- Mom's room number
- Baby's DOB
- Type of birth
- Whether family is going home
- Whether baby is in NICU

Definition of notations on white census board in MBU

- Mom's name listed by last name

- Mom's room number listed to the left of mom's name
- Baby's DOB listed to the right of mom's name. Indicated only as the date of birth not month. Will be listed as 12-(type of birth) indicating baby was born on the 12th
- Type of birth listed as 1 for vaginal and 2 for C-section. This number will follow the DOB. 12-1 indicates baby was born on the 12th and was a vaginal birth
- A heart by baby's DOB and type of birth indicates baby is in the NICU. Check with nurse first before approaching this family
- H= family is planning on going home, see these patients first

HealthONE Sky Ridge:
The white census board is located in the nursery between L&D and MBU on the 2nd floor. The recruiter's hospital id badge will grant access to this room. Moms will either be in the unit on the 2nd floor or in the suites on the 6th floor. Patient rooms are located in MBU on three separate hallways; 2100, 2200 or 2400 numbered rooms. If a patient is in a suite check at the small nurse's desk near the suites with the mom/baby nurse to see if it is ok to approach that patient.

Write on Form:

- Mom's room number
- Baby's DOB
- Baby's time of birth
- Type of birth
- Baby's sex

Definition of notations on white census board in nursery

- Mom's name listed by last name
- Mom's room number listed to the left of mom's name
- Baby's DOB indicated to the right of mom's name
- Baby's time of birth indicated next to date in military time
- Type of birth indicated as V= vaginal and C/S= C-Section
- Baby's sex written as boy or girl
- N= Baby in NICU

HealthONE Medical Center of Aurora:
The white census board is located in the MBU nurse's station on the 2nd floor. There is one unit with rooms numbered from 201-227. There are also three additional rooms where moms may be staying numbered 229-231. Typically these rooms are for those mom's whose baby is in NICU. If a family is not approached before mom is discharged, but baby is in NICU, check with the nurse's to see if mom may be staying in one of these three rooms.

Write on Form:

- Mom's room number
- Type of birth
- Whether family is going home

Definition of notations on white census board in MBU

- Mom's name is indicated by the first 3 letters of her last name followed by a comma and the first initial of her first name (Smi, A for Angela Smith)
- Mom's room number is listed to the left of her name
- Type of birth is color coded: Green= C-section, Black=Vaginal
- H=mom is planning on going home, see these patients first

- BC= Birth certificate has been turned in. This indicates that the family is preparing to go home so even if there is not an H indicating they are going home see this family first

Centura Avista Adventist:
Info. To come

Cases when mom's name is not on white census board:

There are several reasons why a mother's name may not appear on the white census board:

a. Mom may be on another floor
b. She has not been transferred to the MBU unit yet
c. She and baby were discharged
d. Mom was discharged, but baby is still in NICU
e. Mom is a confidential patient and she is listed under a generic last name (typically the last name of the unit director or charge nurse for the day)

If the mother's name is not on the board, the recruiter should check with the nursing staff in the MBU to determine where the mother is located. Sometimes the nursing staff in Labor & Delivery may be able to help locate a mother too. It is extremely rare that you won't be able to find out where a mom is through these resources. Never assume that because a mom is not listed on the board she is discharged. Only count a patient as discharged once that has been determined definitively.

Discharges

If you discover mom has been discharged write "D/C" on the Infant Screening Form and mark a tally on the Daily Tracking Form. Place the screening form in the "Ineligible or Unable to Complete" folder and make sure that sample is discarded at the end of the shift (see below). Check to see whether the discharge occurred with one of the pending samples (in the Pending Folder) or with one of the new blood samples. If it occurred with a new blood sample, look at the baby's date and time of birth to see if the blood was delivered to the utility room late by the scrub techs (baby's DOB or time of birth > 24 hours prior). If it was a pending sample or mom was unavailable for 2+days record this on the racking form under Unable to Complete. If the sample was delivered late record this as Ineligible, late blood from L&D.

Important Notes:

- The recruiter should ALWAYS check with the charge nurse before seeing any patients to determine if there is anyone that should not be approached that day. The recruiter should ask if there are any cases of closed adoptions, fetal demise, illness, or any circumstances for which TEDDY should not approach their patients. The TEDDY recruiter does not need specific information; rather we just need to know if there are any rooms to avoid. If the nurse says to not approach a mom for any reason the recruiter should under NO circumstance approach that mom.
- If a baby is in the NICU or SCN, the recruiter should always check with that mom's nurse to see if the family is ok to approach. If the nurse says it is fine, the recruiter should attempt to see that family first as NICU moms tend to not be in their rooms throughout the day. If the recruiter can not locate such a mom, they can ask the NICU nurses if it is ok to come in and speak to the family in the nursery.
- In the case of a baby being relinquished, the recruiter should check with that mom's nurse to see if it is appropriate to approach her. If the adoption is closed this mom should be counted as ineligible and the sample discarded. If the adoption is open and the adoptive parents will be at the hospital, with an ok from the nurse to approach both families, the recruiter may do so, following procedures for an open adoption.

- If there are ever circumstances in which the recruiter is unsure, they should always check with the charge nurse and/or mom's nurse to determine the most appropriate course of action. The Screening Coordinator and the Assistant Screening Coordinator should always be called or paged if the recruiter has any questions about what they should do in a given situation.

INTERVIEW PROCEDURE

1. Gather the paperwork and organize by the order in which you will visit the rooms. **IMPORTANT**: Prioritize mothers to be interviewed by whether their baby is in the NICU, they are going home that day or not, and pending. These mothers should be interviewed first. Additionally, those who had a vaginal birth should be seen before those who had a C-section when possible. For those at St. Joe's who are Kaiser patients, speak to the Kaiser practitioners about where they would wish you to begin and keep track on their TEDDY log of which patients they have already seen. Approach the patients they have already seen first.

2. Keep track of all Infant Screening Forms by placing them in designated folders during the shift. There are 5 folders to put forms once a disposition is obtained:
    a. New Samples
    b. Completed
    c. Refusals
    d. Ineligibles
    e. Pending

3. Monitor the number of blood samples and the disposition of the interviews during the shift by using the Daily TEDDY Screening Tracking Form. A designated Recruiter will fax this form to the Screening Coordinator at the beginning of the shift every Monday. After faxing a copy the original should be put in the cooler with the blood samples to come back to the BDC. Mark the following categories on the form throughout the shift.
    a. Number of new bloods
    b. Number of pending from previous day
    c. Total number to follow for the day
    d. Number consented during shift
    e. Number Pended during shift (tally marks of reasons for pending)
    f. Number Ineligibles during shift (tally marks of reasons for ineligibles)
    g. Number Refused during shift (tally marks of reasons for refusals)
    h. Observed race of refusers

4. Knock on door and ask if you can enter room. If there is a sign on door, read the sign to make sure you can enter. If sign says "Mother is sleeping" or "Examination in Progress," come back later in shift. If the sign says check at nurse's station before entering, always check at nurse's station first.

5. Introduce yourself as appropriate for the hospital system in which you are working. For Exempla hospitals introduce yourself as being with the research dept. For HealthONE and Centura hospitals, introduce yourself as being from the OB dept and University of Colorado. Briefly explain the study and the newborn genetic screening. Ask if they want to participate. (See Interview Script) Confirm mom's name and date of birth before beginning consent process to ensure you are speaking to the correct person.
    a) Consents:
        i. Definition - parents who agree to participation.

ii. Explain that the consent process takes about 10 minutes and requires going through some paperwork to show we have obtained their permission to do the screening. (Consent form, HIPAA form for Exempla hospitals and Screening form with contact and demographic information)

IMPORTANT: You must complete the consent and HIPAA form first before filling out the Infant Screening Form.

iii. Review each page of the consent form page by page and have one of the parents initial the bottom of each page (except for HealthONE hospitals which only require signatures on pages 5 and 6). After completing the entire consent form, ask the parent(s) to summarize the purpose of the study in 1-2 sentences. Have parent(s) sign the final page of the form. Answer any questions the parent(s) my have. The Recruiter signs the form too and gives parent(s) the pink copy of the consent form.

iv. Inform the parent(s) that they should receive the genetic screening results within 8 weeks. If they have not heard from us at this point in time, they should call us. Draw attention to the brightly colored flyer attached to the last page of the parent's copy of the consent form. Point out the phone number where they can call us.

v. **IMPORTANT**: Families that do not currently live in Denver Metro Area/Front Range or who will not be living in area when screening results come in are still eligible for *screening*. However, at the time that screening consent is obtained, if parents indicate that they do not live in area or will move away from area, they must be told that this would make them ineligible for the follow-up study, even if they meet the genetic eligibility criteria. However, we will still contact them with an explanation of their genetic screening results.

vi. Exempla Hospitals Only: Review and explain the hospital's HIPAA form. Have the parent sign the form. Give parent(s) yellow copy of HIPAA form.

vii. Fill out Infant Screening Form.

viii. If the parents can not provide a phone number at this point, explain to them that we can not do the screening without a phone number. This is necessary only to ensure we have means of contacting them should results be returned to us, or their child is eligible for the follow-up. If they can not/will not provide a phone number politely decline screening and shred the consent and screening form.

ix. Place copies of completed paperwork in Completed Folder.

b) Refusals:

i. Definition - parents who indicate the have no interest in participating.

ii. If the parents verbally refuse, ask if there are any questions you can answer about the screening. Tactfully try to clarify misconceptions they may have and see if they may change their minds.

iii. If they still say "no", thank them for their time and leave the room. Make a note with reason for refusal on the Screening Form and place the Form in the Refusals Folder. All refusal forms will be shredded at the end of the shift and a mark should be made on the tracking form indicating the number of refusers and their observed race.

c) Ineligibles:

i. Definition – Situations where mom does not speak fluent English (with the exception of Spanish speakers with Spanish speaking recruiters at St. Joe's, MCA and Avista), infant is too sick, fetal demise, no label on blood sample, mom is 16 or 17 years old but does not have an witness to co-sign who is 18 years old or older, close adoption, etc.

ii. If the parents meet the ineligible criteria, make a note on the Infant Screening Form and place the form in the Ineligibles Folder. Mark a tally on the daily tracking form.

All Ineligible forms (which contain PHI) will be shredded at the end of the recruiter's shift and will not be given to the TEDDY Study staff. Only the aggregate data noted on the daily tracking form will be shared with TEDDY.

d) Pendings:
   i. Definition – Situations when the baby is born after 4am, mom has not been transferred from L&D unit yet, mom is sleeping, mom is unavailable or with doctor or nurse, or mom/dad asked recruiter to come back the next day.
   ii. Recruiter should make several attempts (at least 3) to check mom's room during the shift (especially if mom is being discharged that day). Spread out the attempts throughout the shift. Don't go back 3 times in 30 minutes and consider that family as pending.
   iii. Write a "P" with dark circle around it at the top of the Infant Screening form and make notes about reasons for the pending status and how many times room was visited.
   iv. Place form in the Pending Folder at end of the shift if unable to complete. Mark a tally on the daily tracking form indicating the reason for the pending.

POST INTERVIEW PROCEDURE

1. Once all the interviews are completed, go back to the nurse's station to organize the paperwork. Go through paperwork and check to make sure all forms are filled out completely. Forms are not complete unless:
   a. Each page has parent initials at the bottom (for applicable hospitals) and parent signatures on Page 5 and 6.
   b. There are 6 pages of the consent form and for Exempla hospitals 2 HIPAA pages. In other words, every page is accounted for and nothing is missing.
   c. The recruiter has signed the appropriate pages.
   d. INFANT SCREENING FORM: Each field is filled in or marked appropriately on the Infant Screening Form. If the family has said No to long term storage this is written on the top of the Screening Form. If the patient is an FDR this is very clearly marked on the top of the page as well. The baby's name on the screening form matches the baby's name on the consent form. There is a correct address and phone number for the family. **THERE SHOULD BE NO MISSING INFORMATION ON THE SCREENING FORM.**

   If any information, pages of the consent or signatures are missing, the recruiter must go back to the family's room to obtain the necessary information. NO consent or screening form should come back to the lab with missing information.

2. For those who consent to screening, separate the paperwork into 2 piles: one for the TEDDY Study and one for the Hospital (see shaded columns in chart below).
   a. Exempla: Take 3 labels from the **mother's** chart and place one label on the first page (upper right corner) of the hospital's copy and one label on the first page of Teddy's copy of the informed consent. Place the third label in the bottom right corner of the first page of the hospital's copy of the HIPPA form.
   b. HealthONE and Centura: Take two labels from the **mother's** chart and place one label on the top of the first page of both the hospital copy and TEDDY copy of the informed consent.

		Distribution of copies for participants who consented		
	# of pages	Hospital	TEDDY	Participant
Informed Consent	6	White copy	Yellow copy	Pink copy
HIPAA (Exempla)	2	White copy	----	Yellow copy
Infant Screening Form	1	----	Only copy (white)	----

3. Keep the paperwork for the refusals, ineligibles, and pending in their designated folders. See the instructions in next section (Cord Blood Processing).

Cord Blood Processing

1. Return to utility room and put on gloves. Process the blood samples in the following order:
    a. Consented
        i. Gather all the cord blood samples with completed interview paperwork and prepare them for transport to the TEDDY lab. Place the cord blood tubes in a new biohazard plastic bag and roll up the corresponding paperwork (yellow copy of consent form and Infant Screening Form) and place in the transport cooler bag. Leave in the cooler's designated area. A TEDDY Lab staff employee will stop by on designated days to pick up the samples.
        ii. Take the copies of the hospitals paperwork to the designated area for filing.
    b. Pendings
        i. Double check names on the forms against the names on the tubes of blood. Put the "pending" cord blood samples in the bin labeled "pending" for the next day's recruiter.
        ii. File the form back in the "Pending folder" and leave in designated area for the next day's recruiter
    c. Refusals & Ineligibles
        i. Double check the mother's names on the Infant Screening Forms against the name on the tubes of blood. Throw away the cord blood samples in the sharps container for those moms/parents who declined participation.

            IMPORTANT: Be very careful to make sure you are throwing away the correct samples. Accidents do occur and you don't want to throw away a blood sample for which you've just obtained consent. For this reason, **always** process the blood samples in the specific order listed above, processing those who have refused last.

After all samples are processed accordingly, shred the Infant Screening Form for those who refused, were ineligible or unable to complete. Do not collect any information for these individuals except reason for ineligibility, refusal and observed race. Make tally marks of these data points on the Daily Tracking Form. This information is collected only in aggregate as a means of tracking the rate of refusals and to determine problems with the screening and recruitment process.

Tracking Form: At the end of the shift, recruiters are expected to double count and compare the number of blood samples with the Infant Screening Forms. All names must add up and the subsequent tally marks on the tracking form must add up correctly. Double check to make sure that the tally marks all add up to the total number to follow for the day.

SCREENING QUALITY ASSURANCE

Several methods are used to monitor and evaluate the screening procedures to assess whether the goals and objectives are being met. Goals and objectives will be reviewed with each recruiter from the outset as well as the methods and measures for the quality assessment. Various objective methods will be used to evaluate progress and will be supplemented with subjective feedback from meetings with recruiters.

Screening goals and objectives

1. To obtain cord blood samples on 90-95% on all hospital deliveries.
2. To approach 90-100% of parents for whom a blood sample was collected.
3. To reach an overall consent rate of 85-90% of all parents approached for participation in the newborn genetic screening.

Methods

1. Observation (every 3-6 months as needed)
2. Daily Tracking Form (reviewed weekly and monthly)
3. Individual monthly efficiency tracking (by tracking forms)
4. Staff meetings and other feedback (every month 2-3 months or as needed)

Performance measures – reviewed monthly

1. Number of blood samples collected
2. Number of families approached
3. Number of families consented
4. Number of samples left pending
5. Number of blood samples followed

Performance feedback – every 3-6 months as needed

1. All recruiter group meeting- every 3 months or as needed
2. Individual performance evaluations- annually or as needed

DISENROLLEES / DROP-OUTS

The following procedures will be followed when participants who have initially agreed to screening, but later decide to revoke their consent for participation in the genetic screening. All appropriate measures will be taken to immediately locate and stop the processing of the samples, to identify the databases (local and DCC) and the shipping logs referencing the sample, and most importantly, to stop the release of a Results Letter. Additionally, necessary efforts will be made to correspond with the requesting study participant until the sample is destroyed. These procedures will be followed for both hospital-based and clinic-based screening.

Steps

1. The Screening Coordinator or another TEDDY study manager will speak to the study participant to explain how their request will be honored. The participant will be informed of the process required to locate the sample and that the screening process will be stopped at the point in which the sample is located. They will also be cautioned that depending on where the sample is in the process, they may receive a Results Letter before we are able to determine the sample's location. We will advise participants' to tear up the letters without reading them in these cases.
2. The Screening Coordinator will immediately notify the Lab Coordinator verbally and through email of the situation and provide the Local Code and TEDDY code for identification purposes. The Lab Coordinator will identify whether or not the sample has yet been shipped to Roche for processing.
    a. Sample still at local lab:
        i. STEP ONE: If the blood sample(s) has not yet been sent (including any processed for long-term storage), they will be pulled and discarded. All associated lab paperwork and tracking forms will be marked with a line through them and a note indicating the date and "Participant Drop-Out."
        ii. STEP TWO: Next, the Lab Coordinator will notify the local Database Coordinator(s) of the drop-out. If the data has not been uploaded to the DCC yet, the record will be deleted from the Screening Database. If it has been uploaded, the DCC will also be contacted to remove the record from their database.
    b. Sample already sent to Roche:
        i. STEP ONE: If the sample has already been sent to Roche, the Lab Coordinator will contact Roche to notify them to pull the sample from the pre-processed or post-processed batch. If it has already been processed, they will be instructed to remove the lab result from the data results report that is sent to the local Colorado site. In place of the lab result, they will enter a dummy code to notify the Database Coordinator of the drop-out status of the participant. This code will also allow Roche to be paid for the lab processing, while keeping the local site from mailing the results letter.
        ii. STEP TWO: The appropriate steps will be followed on the DCC website to mark the subject as "participant withdrawn from screening."
3. The Lab and Database Coordinators will communicate the outcome of their efforts to the Screening Coordinator, who will in turn contact the family to give final word that the sample has been destroyed. A follow-up letter will be mailed to the parent(s) as documentation that their request was fulfilled. A separate paper file will be kept by the Screening Coordinator to include the original screening consent form and contact information and subsequent notes or letters referencing each case. This file will be kept under lock and key and with limited access to study personnel.

GENERAL POPULATION SCREENING PROCEDURES – CLINICS

Infrequently, families will be referred to the study by means other than participating hospitals. These families have two options for the genetic screening: a) cord kit, or b) heel stick procedure. The procedures for these options will be similar for the First-Degree Relative Cohort in the next section.

Cord Kit

A TEDDY staff person would discuss the study with the interested parent(s). If parents choose to participate, the staff person will follow the procedures in the *FDR Genetic Screening Procedures: Unborn Child* Section below. A notebook of participating families will be kept by a clinic staff member to track due dates and incoming blood samples.

Heel Stick
Similarly, if the baby is already born or the parents chose to wait until after the baby's birth for the testing, the TEDDY staff person would discuss the study and heel stick procedure with the parent(s). For participating parents, the staff person will follow the procedures in the *FDR Genetic Screening Procedures: Child Less Than 3 Months of Age*

FIRST-DEGREE RELATIVES SCREENING PROCEDURES - CLINICS

To meet First-Degree Relative (FDR) screening and recruitment goals, the Colorado site will partner with health professionals working directly with people with T1DM to identify newborns eligible for TEDDY screening. The term "clinics" will refer to all medical settings providing care to patients, including larger clinics and independent practices. Screening strategies will vary, based upon the structure of each health setting. Clinics will include, but are not limited to, the following:

	Target Audience	
	Adults with T1DM expecting a baby or have a newborn < 3 months	Parents of a child with T1DM, and are expecting another baby or have a newborn < 3 months of age.
Diabetes Clinics	X	X
Adult Endocrinology Clinics	X	
Pediatric Endocrinology Clinics		X
OB/GYN Clinics	X	

FDR Eligibility Criteria Questions:
The following questions will be used to identify FDR newborns (offspring or sibling) that would be eligible for TEDDY Study screening:

Diabetes Clinics:
- Is patient expecting a baby? (*question applies to men and women*)
- Does patient have child less than 3 months old?
- Is a parent of a child patient expecting a baby?
- Does patient have a brother/sister less than 3 months old?
- Is the sibling a full or half sibling?

Adult Endocrinology Clinics:
- Does patient have child less than 3 months old?
- Is patient expecting a baby? (*question applies to men and women*)

Pediatric Endocrinology Clinics:
- Does patient have a brother/sister less than 3 months old?
- Is the sibling a full or half sibling?
- Are patient's parents expecting a baby?

OB/GYN Clinics:
- Does expectant mother or biologic father have T1DM?
- Does expectant mother have another child with T1DM?

IMPORTANT: Only full siblings of someone with T1DM are considered in the FDR Cohort. Half-siblings of someone with T1DM are to be considered for screening in the general population cohort.

FDR Genetic Screening Procedures

Newborns with a first-degree relative can enter the study in a couple ways. Most of the time, parents of the newborn (or undelivered baby) will be self-referred to the study after hearing about the study from their physician, clinic staff, word-of-mouth, or in written format from fliers, posters, etc. Parents may also be approached with the opportunity to participate either at the hospital (captured through the general population newborn genetic screening method) or at a clinic (only after signing a HIPAA form indicating a study can approach them).

UNBORN CHILD:

If a FDR expectant mother or father agrees to participation in TEDDY screening, the following procedures will be done to complete the screening process for an umbilical cord sample:

a) Discuss study with patients/parents. (see interview script)
   NOTE: Informed consent must be obtained before filing out screening form.
b) Review TEDDY FDR Screening Consent Form with parents. This includes:
   - Explaining the consent process
   - Reviewing each page of the consent form page by page.
   - Have the parent initial at the bottom of each page
   - Answer any questions the parent(s) may have.
   - After completing the entire consent form, ask the parent(s) to summarize the purpose of the study in 1-2 sentences.
   - Have parent(s) sign the final pages of the form. If only one parent is present, a reasonable effort will be made to get the other parent's authorization.
   - Recruiter signs the form and gives a copy of the consent form to parent(s).
c) Inform the parent(s) that they should receive the genetic screening results within 8 weeks. If they have not heard from us at this point in time, they should call us. Draw attention to the brightly colored flyer attached to the last page of the parent's copy of the consent form. Point out the phone number where they can call us.
d) Complete the Infant Screening Form
e) Give parents the following as a part of the cord blood kit to arrange for the collection newborn's cord blood at the time of birth:
   - Red & purple-top evacuated tubes in a sealed packet
   - Postage-paid box addressed to the TEDDY Study (used to send cord blood to TEDDY site after birth)
   - Letter/instructions for the delivering physician
   - Letter/ instructions for expectant parents
   - Copy of signed Screening Consent Form

   The following script can be used to verbally explain the cord blood collection process to the parents:

> "This cord blood collection kit should be taken with you to the hospital when you are going to give birth. Included is a letter to give to your physician about the cord blood collection and a copy of your signed consent, so that your physician knows that you agree to participate.

When your baby is born, the hospital staff will collect some cord blood as a part of their standard procedures. At this time, they will also collect cord blood for the TEDDY Study. This process is painless for your baby. When you leave the hospital, the staff will give you the tubes of your baby's cord blood. You can put these in this box addressed to the TEDDY Study and put it in the mail. You should do this within 2-3 days of your child's birth. When we receive the blood, we will begin the genetic screening to determine your child's risk for Type 1 diabetes. Have I missed covering any information you think is important?"

Mailing of cord kit

If staff person is unable to meet with parents in person to review the consent form and hand out the cord kit, the appropriate materials will be mailed to the parents within about 4-6 weeks of the baby's due date. The staff person will call the parents about 1 week after the materials are mailed to go over the consent form, instructions for collecting the blood sample, and explain carefully what materials need to be mailed back to TEDDY. The staff person will make sure to answer all questions and advise the family on any concerns they may have.

CHILD LESS THAN 3 MONTHS OF AGE:

Newborns who meet the criteria for the FDR cohort are also eligible for screening if the baby is between the ages of 1 day and 3 months. These newborns can have a blood sample collected using the standard heel stick procedure. It is important that the heel sticks be done as early as possible (before 3 months of age is preferable; 3 months is the absolute latest). This timing allows for a 4 month clinic visit for the follow up study is the child is identified at higher risk.

This procedure can be conducted at the TEDDY clinic or one of the clinical sites depending on clinic resources and staff availability. Parents must complete the consent process as described above (steps a-d) prior to the heel stick procedure. When completing the Infant Screening Form, the TEDDY staff member must CLEARLY write the baby's age at the top of the form. If the baby is 2 ½ - 3 months of age at the time of the heel stick, the sample must be rushed to the lab with follow-up to notify them the sample must be processed urgently.

Heel Stick Procedure

About 8-10 drops (less than ½ teaspoon) of blood will be drawn from the infant's heel and will be collected in a 5 mL purple-top bullet. If the parents agree to the long-term blood storage consent, two bullets will be collected (if there is adequate blood flow). The new born will not be poked more 2 times in an attempt to draw blood.

Equipment

- 70% isopopyl alcohol prep wipes
- Gauze
- Sterile lancet (Quikheel ™ or Tenderfoot ™ are commonly used)
- Heel warming device
- Collection devices (Microtainers or 'bullets')

Process

1. Apply a warming device to the infant's heel approximately 3 minutes before the skin puncture to increase the blood flow. I.e. infant heel warmer.
2. The site to be used for the heel stick should be pink or normal color, and free of scars, cuts,

bruises, or rashes. Do not choose a site that is cyanotic (bluish in color) or edematous (swollen).
3. Clean the site with an alcohol wipe. The site should be completely dry before the skin puncture.
4. Open the sterile lancet and remove from packaging right before puncture. Don gloves before grasping the foot in a firm but gentle hold by wrapping fingers around the bottom of the heel and around the top of the foot.
5. Position the lancet device on the site firmly applying gentle pressure, this assists in decreasing the sensation and ensures the puncture depth is adequate. Puncture the heel on the on the sole of the foot with the Quickheel lancet device, dispose of the device in a sharps container.
6. Apply gentle pressure to the site while wiping away the first drop of blood on a dry piece of gauze.
7. Position the infant's foot downward to enhance blood flow and continue to apply gentle pressure to the tissue surrounding the heel puncture site. It is important NOT to squeeze or massage vigorously as this introduces excess tissue fluid in the specimen that could cause hemolysis.
8. Collect the blood in appropriate microtainers (per Lab Protocol) by scooping the drop of blood and allowing the blood to run down the walls of the bullet. Do not scoop blood against the skin surface; it activates platelets which can cause hemolysis.
9. Tap the tube gently to encourage the settling of blood to the bottom of the tube. Cover the bullets with the cap and gently invert the bullets. Once collection is complete, apply pressure to the heel site with clean gauze until bleeding stops, then apply bandage.
10. Label the specimens per Lab Protocol, dispose of contaminated materials in the sharps box, throw away opened materials not used, remove gloves, and wash hands.

Clinic Orientation/Strategy Development
As the Screening Coordinator establishes FDR Screening partnerships with different health clinics, as described in Future Considerations below, it is necessary to work with clinic staff to establish a strong screening system for that setting.
Key considerations when establishing a recruitment system within a health care setting include the following:

- Educate staff about TEDDY Study, including purpose, eligibility criteria, and overview of protocol.
- Work with current clinic staff to understand existing clinic process. It is important to integrate TEDDY screening into the existing clinic process to ensure an undisturbed clinical care routine and efficiency for patients and staff. Developing buy-in from the staff and physicians is the only way screening will succeed.
- Work with clinic staff to understand privacy practices and to establish a system compliant with current HIPAA and COMIRB regulations.

CLINIC-SPECIFIC STRATEGIES

Barbara Davis Center – Young Adult Clinic
The Barbara Davis Center (BDC) clinic provides comprehensive programs and services to over 2,000 children and adults with T1DM and their families in the Rocky Mountain Region. The BDC young adult clinic (YAC) and pediatric clinic (PEDS) are the first FDR screening recruitment sites for Colorado. Screening recruitment for TEDDY was initiated at this site due to an existing recruitment strategy for the DAISY Study and the potential of encountering a large number of FDRS due to the high volume of T1DM patients. A Study Recruiter was hired to ensure full-time availability for screening efforts in the BDC/YAC.

The current recruitment process encompasses the following procedures to ensure each eligible patient is given the opportunity to have his/her infant screened. This will help ensure 100% accuracy in reaching all patients, as well as making it easier to quickly identify interested patients. The basic patient recruiting procedures include:

1. At the beginning of each clinic day, review clinic schedule. This can be found on the Clinic Staff Schedule board in the PRA Office, or the electronic board on the pediatric side.
2. Review scheduled patients' records in the Pink Panther Database to find the following information:
    a. HIPAA Authorization A Status – This information is found on the Demographic/Ins Screen in the Pink Panther Database. The HIPAA Authorization A: Research Recruitment form is given to clients to learn of their interest in participating in research studies
    b. Patients will have one of the following options identified in this section:
        i. Yes – indicates patient is willing to be approached about research studies
        ii. No - indicates patient is not interested in research studies
        iii. Blank - indicates patient has not had opportunity to sign HIPAA Authorization A and will see the form before current day's appointment.
    c. Patient Age – Patient date of birth is found on the Demographic/Ins Screen in the Pink Panther Database. This information will identify whether the patient is of childbearing age.
    d. Pregnancy Status List – Review pregnancy status list
3. Identify if the patient should be approached to learn whether he/she has a child eligible for TEDDY Screening. The patient is considered eligible to be approached if he/she has consented to HIPAA Authorization A form and is of childbearing age.
    a. Patient eligible:

If the HIPAA Authorization A field in Pink Panther is "yes" and if they are of child bearing age (and/or if they are already on the pregnancy status list).

b. Patient eligibility undetermined
For those patients for whom the status of HIPAA Authorization A is not yet determined (i.e. the field in Pink Panther is blank), the TEDDY Recruiter will need to check the patients' file after he/she has completed the check-in process to see if the form was signed to determine next step.

c. Patient not eligible
Patients are not eligible if the HIPAA A field is "no", if the patient is not of childbearing age, if the patient just lost a pregnancy, and/or if the physician indicates it is not a good opportunity to approach the patient.

4. The recruiter should work with the clinic staff to determine the most optimal time during an appointment to approach a patient. Potential opportunities to talk with patients include:
   a. Before Check-In: If there is a wait and the patient has already signed the HIPAA Authorization A form. If the patient has not yet signed the HIPAA Authorization A form, recruiter must wait until the patient has had the opportunity to do so and learn the status of that choice, to ensure patients are not inappropriately approached.
   b. After Check-In: While the patient is waiting to see the nurse.
   c. In between clinic staff: After the nurse visit while the patient is waiting to see the physician.
   d. At the end of the appointment: After the physician has completed the patient's visit.

   NOTE: It is important not to interrupt the natural clinic flow. If the Recruiter is talking to the patient about TEDDY, and part of his/her clinical care team comes in for part of the patient visit, the TEDDY Study Recruiter should stop and continue during the next gap in the patient's visit.

5. Based upon the patient's due date, different steps will be taken to discuss and consent patients for the TEDDY Study.
   a. Patients 8-9 months pregnant - TEDDY Study Recruiter will explain the study to the parent(s) and answer any questions. If parent(s) agree to participate and want to complete the consent process during the clinic visit, the recruiter will follow the steps described in FDR Unborn Child Section above. If the parents want to take the materials home to review, the recruiter will get their contact information and agree upon a time to follow up with within 1 week on the phone. The Recruiter will continue to follow up with the parent(s) until they either decide not to participate or they consent to screening.
   b. Patients 5-8 months pregnant - TEDDY Study Recruiter will tell the patient about the opportunity for the newborn to participate in the TEDDY Study. If the patient is interested, the TEDDY Recruiter will give the patient TEDDY information and will enter them in a tracking database to ensure that the patient is approached at 8 months during the pregnancy to sign the screening consent and receive the cord blood kit.
   c. Patients <5 months pregnant – TEDDY Study Recruiter will not actively approach these patients unless a BDC YAC Clinical Staff person initiates the conversation about TEDDY. If this occurs, the recruiter will discuss the study in brief terms, answer any questions, and let the patient know that we will follow up when the pregnancy is further along. The Recruiter will add the patient's name to the tracking database to contact in the future. The patient will be given a screening brochure (when available) and contact information for the study.

   NOTE: Although it is desirable to identify all potential participants as soon as learning of their pregnancy status, care must be taken to ensure sensitivity to the high risk nature of many of these pregnancies. Moreover, past history with DAISY has shown that recruiting for the study too early

decreases participation rates. Therefore the Recruiter will actively pursue potential participants after the pregnancy is in its 5 month (>20 weeks).

Recruitment Tracking

The recruiter will keep a log book to record the patients who are expecting and their due dates, patients (or parents of patients) who are planning a pregnancy, patients who have declined participation, and finally patients who are ineligible for the screening.

The Study Recruiter will also note all patient contact information on a Data Tracking Form (monthly tracking). The form will keep track of the:

- Number of potential FDR subjects each month
- Total consented each month
- Number pending each month
- Number of ineligibles each month
- Number of refusals each month

Barbara Davis Center – Pediatric Clinic

Two nurses in the BDC Pediatric Clinic function as the primary point-persons for recruiting and screening newborns. To maximize efficiency and ensure near 100% compliance, a form was created to assess families' interest in the study. This check-in form is handed out to every family as they check-in to the clinic for their appointments. They simply mark whether they are interested in learning more about the TEDDY Study, and if yes, they answer a few questions to determine eligibility.

If a family is determined to be eligible, the form is flagged at set aside for the key nurses to review. They will talk to the families about the study. If the family is interested in participating, they will hand out brochures, fill out a referral form to send to the TEDDY Screening Coordinator, administer the informed consent, or hand out a cord blood kit packet (all depending on the age of the newborn or the gestational age of the pregnancy).

The Screening Coordinator, the key nurses, and the BDC Pediatric staff work closely to catch all eligible families and promote the study.

HLA PROCESSING

HLA typing: Cord Blood Processing, Storage and Shipment

Cord Blood Processing

1. Cord bloods need to be processed in a timely fashion. Samples can only be left for a maximum of two days before processing, with the exception of unresolved pendings, which can be left for a maximum of two weeks. If the blood remains unprocessed for a longer amount of time, the sample becomes hemolyzed and does not retain its integrity.
2. If, due to illness or emergency, samples could not be processed by the responsible recruiter in a timely fashion, the recruiter should alert the other recruiters, the recruiter supervisor, and lab personnel so that the blood can be processed on time.

Lab Preparation

Before processing any sample, it is important to do the following to protect yourself and the samples:

1. Prepare a clean field to work on by wiping the counter with a clean Sani-cloth (germicidal disposable cloth).
2. Wash your hands and put on a fresh pair of gloves.
3. Take out clean racks for vacutainers and cryovials. Clean all dirty racks in 10% bleach/water solution.

NOTE: Everyone is responsible for cleaning up after themselves. We have to work together to maintain a clean working environment.

Precautions

There are a number of precautions to take when processing blood samples.

1. **DO NOT** uncap more than one person's sample at a time!!!!
2. Place a Label for each tube with the TEDDY ID as each hospital ID is removed.
3. When placing a cryovial cap onto the counter, make sure it is open-side up!!!
4. Wipe your gloves clean with a Sani-cloth after working with each individual cord blood. Do not allow blood to collect on your gloves.
5. Clean the outside of bloody vacutainers before processing.
6. Uncap vacutainers away from yourself. Masks and shields are available to use for further spray protection.
7. Maintain a consistent method of filling cryovials. Collect as much of the sample as possible; fill the vials between 0.5ml and 1.25ml marks. Try not to overfill the vials.

Processing Blood Samples

A lavender-top vacutainer should be kept at room temperature until it can be processed. Once samples are received at the TEDDY Clinical lab, a local ID is assigned to each subject. The appropriate information, from each subject's screening form, is entered into the DCC screening enrollment database and a TEDDY number is assigned. Tube labels are generated which include the subject's local ID, date of draw, as well as TEDDY ID.

1. Collect a whole blood sample for HLA typing (these samples are shipped every two weeks).
   a. Place the label on a 2mL Sarstedt cryovial
   b. Gently agitate the lavender-top vacutainer back and forth, about four times
   c. Aliquot 0.5mL of whole blood from the lavender top tube into the 2mL Sarstedt vial.
   d. Store the sample in the cryobox at 4˚C until it is sent to the HLA lab.

e. Every two weeks a "packing list" is generated for the samples to be sent for HLA typing. Double check the packing list with the samples in the cryobox. Print out a copy of the packing list, to be mailed with the samples, email a copy to the DCC and to the HLA lab.

2. Collect a whole blood sample for back-up and QC purposes.
   a. Place the label on a 2ml Sarstedt cryovial
   b. Aliqout 1.25ml of whole blood from lavender top tube into cryovial
   c. Store sample in appropriate box at 4˚C.

3. Centrifuge blood to separate whole blood into 3 layers: top layer (clear yellow) is plasma, middle layer (white) is the buffy coat or white blood cells, and the bottom layer (red) is red blood cells.
   a. Balance the lavender top tubes in the centrifuge
   b. Spin for 10 minutes at room temperature or 4˚C in swinging bucket (preferred) or fixed angle rotor at 1500 to 1800 RCF (Relative Centrifugal Force).

4. Collect separated layers into labeled cryovials
   a. Using a transfer pipet, aliquot no more than 1.25ml plasma into one cryovial. Discard the rest of the plasma. This sample will be stored at -20˚C.
   b. Using the same transfer pipet, collect the buffy coat with some red blood cells, to add volume, up to 750ul. Transfer into labeled cryovial. This sample will be stored at -20˚C.
   c. Using the same transfer pipet, collect up to 1.25ml red blood cells (RBCs). Transfer into labeled cryovial. This sample will be stored at -70˚C.

TEDDY Cord Blood Storage

1. Aliquot 0.5ml in 2ml cryovial-sent to Roche for HLA typing
2. Aliquot 0.5 ml in 2ml cryovial, stored at 4˚ in "6" box
3. If storage consent not given, this sample is only kept until we have HLA results

<u>The following procedure is completed only if the subject's parent(s) has given consent for blood and DNA storage</u>

1. Tubes are spun to separate blood components
2. Aliquot plasma into 0.5ml cryovials. Store at -70.
3. Collect buffy coat and red blood cells to volume of approximately 750ul into 2ml cryovial. Store at -70.

TEDDY Cord Blood Shipping

Every two weeks, cord blood samples will be shipped to Roche for HLA typing. As the samples are processed they are stored in a 6" Nalgene box at 4˚C, with the last row in the box reserved for FDR samples.

When ready to ship, go to the TEDDY website, click on "Sample Shipment System" (located under Data Management on the left navigational toolbar). Enter the date of shipment and choose "HLA Screening Lab". Enter the Subject ID of each sample that you will be sending to Roche. After entering all of the Subject IDs click on "Create a shipping list". Save the shipping list to a local database, print the shipping list and send it in the box containing the samples.

Put the Nalgene box(es) containing cord blood samples in an appropriate cool storage shipping box (i.e. Styrofoam container within a cardboard box) include the shipping list and a cold pack. Ship the container overnight to the screening lab.

A2. Site Specific Screening Procedures: Finland

Recruitment*:*
Following the practice developed for the DIPP study, the investigators will continue to screen all babies born in the cities of Turku, Oulu, and Tampere (approximately 11,000 births annually) using HLA Class II screening modified to reflect TEDDY eligibility criteria.

Recruitment Locations are:

1) Turku University Central Hospital
Department of Pediatrics
Kiinamyllynkatu 4-8
FIN-20520 Turku

2) Tampere University Hospital
Department of Pediatrics
Teiskontie 35
FIN-33521 Tampere

3) Oulu University Hospital
Department of Pediatrics
Kajaanintie 50
FIN-90220 Oulu

Consent:
An extra cord blood sample for TEDDY screening is collected after delivery from all newborn babies by the delivery room personnel in the three recruitment hospitals, when cord blood is drawn for routine screening for congenital hypothyroidism. TEDDY Research Nurses contact parents at the Maternity Unit the day after delivery. Parents are given verbal and written information about TEDDY study and Type 1 Diabetes. After written parental consent, the cord blood samples are screened for genetic HLA-conferred risk to later develop Type 1 Diabetes. If the parents are not willing to participate, the blood sample is destroyed.

Blood Collection and Handling

Cord blood is drawn with a syringe and needle inserted into the cord to collect as much blood (1-15 ml) as possible. In Turku, the blood samples are delivered on every working day directly to the TEDDY screening laboratory within the hospital area, where blood spots are prepared for genotyping. In Tampere and Oulu, blood spots are prepared in the local TEDDY laboratory and mailed to the screening laboratory once a week.

Part of the blood is dropped on the filter paper of the TEDDY Screening Remittance with the local subject ID number printed on it, and left on the bench to dry at room temperature for 2 hours. The Remittance is then placed into a plastic cover to keep it free from dust and moisture, and stored at room temperature in binders. The information on the Remittance is entered into the TEDDY DCC Registration form.

Small circles from the dried blood spot samples are punched into 96-well microtiter plates used for PCR reaction. Bar code labels on the filter paper are simultaneously read to the computer to create a database of samples. First genotyping includes hybridization reaction with amplified DQB1 gene segment using a series of sequence specific oligonucleotide probes labeled with various lanthanide labels. Further stepwise genotypings include further DQB1 typing as well as DQA1 and DRB1 typing, when informative. The results are transferred to the DCC and simultaneously also to the personnel of the screening site.

A3. Site Specific Screening Procedures: Germany

Obtaining Informed Consent
Screening is done in different locations within our Munich Clinical Center, such as hospitals and clinics/physician offices. Depending on the screening location, informed consent is obtained **face to face or by telephone and mail**.

First degree relatives:
As most of the families with first degree relatives with type 1 diabetes are not located in Munich, informed consent has to be obtained most times by telephone and mail. In that case, the TEDDY screening consent form is sent to the family together with a prepaid envelope for resending the signed consent form, before the consent process (see below) is done by telephone. Informed Consent is obtained by TEDDY nurses or nutritionists working in the TEDDY study.

General population:
Screening of general population families is explained during a pre-delivery visit.
The family will bring the signed consent form with them to the delivery and the midwife will collect the signed consent form or the signed consent is filed with other documents in the patient chart.

Procedure of obtaining informed Consent:

1. Explain that the consent process takes about 5 minutes.
2. Review each page of the TEDDY consent form. After completing the consent form, answer any questions the parent(s) my have. Have parent(s) sign the final page of the form (in case this is done by phone, ask the parents to send the signed form back by mail).
3. Inform the parent(s) that they should receive the genetic screening results within 6-8 weeks. If they have not heard from us at this point in time, they should call us. Point out the phone number where they can call us.

Screening process, providing materials to parents and answering questions.

Recruitment of families:

First degree relatives are recruited all over Germany through a network of hospitals (obstetric and diabetes departments) and pediatric general practitioners who have been collaborating with us for 15 years in the context of the BABYDIAB and BABYDIET-study. Expecting mothers of babies who have a first degree relative with T1DM are informed either through this network or through advertising in a nationwide information network (diabetes newsletters, brochures, internet, pregnancy newsletters).

Participants of the general population are recruited pre-delivery in 5 obstetric hospitals located in Munich:

- Hospital Rechts der Isar / Technical University Munich

- Hospital Dritter Orden
- Gynäkologische Abteilung Hospital Klinikum Großhadern / Ludwig Maximilians-University Munich
- Frauenklinik Maistraße / Ludwig-Maximilians-University Munich
- Hospital München Schwabing

Mothers are informed about the screening at the hospitals information-day for pregnant mothers by the TEDDY screening coordinator and at their pre-delivery-examination at the hospital by obstetricians.

Providing materials to parents:
First degree relatives: First degree relatives participants are sent the following materials as a part of the cord blood kit to arrange for the collection newborn's cord blood at the time of birth:

- EDTA-tube in a sealed packet
- Postage-paid box addressed to the TEDDY Study (used to send cord blood to TEDDY site after birth)
- Letter/instructions for the delivering physician
- Letter/ instructions for expectant parents
- Brochure
- Copy of signed Screening Consent Form
- Screening questionnaire

General population:
The following materials are provided to participants of the general population at a pre-delivery visit, done by a TEDDY nurse, or in some hospitals materials will be provided by hospital staff (obstetricians or midwifes):

- Brochure
- Copy of signed Screening Consent Form
- Screening questionnaire

Answering questions
Questions of interested families concerning the screening or other parts of the Teddy study will be answered at the pre-delivery visit or by phone. The list of FAQs will assist recruitment staff in answering questions.

Collection, Processing, and Shipment of the blood sample for HLA determination

Collection of blood samples:

First Degree Relatives:
Collection of cord blood samples at the time of delivery:
FDR participants, who are not located in Munich, will organize the collection of cord blood samples with their obstetric clinic. EDTA-tubes for collection of cord blood at the time of delivery are sent to the families before delivery. Delivery room personnel

(obstetrician or midwife) will drop 2 ml cord blood directly from the cord in a collecting EDTA (lavender) top tube according to written instructions. The tube is labeled with the name and the birth date of the child. Families will immediately send the cord blood sample together with the completed screening questionnaire to our Munich lab by prepaid envelopes.

Collection of venous blood samples if child is less than 4 months of age:
Newborns who meet the criteria for the FDR cohort are also eligible for screening if they are between 1 day and 4 months of age. These newborns can have a blood sample collected by venous bleeding. This procedure can be conducted at the pediatrician's office. Parents will complete the consent process as described above prior to the bleeding and will get a letter with instructions for the pediatricians.

General Population: If the mother has signed informed consent pre-delivery, cord blood samples are collected by delivery room personnel (obstetrician or midwife) who are instructed in the procedures by TEDDY personnel. Written TEDDY instructions are available in each delivery room. Delivery room personnel will drop 2 ml cord blood directly from the cord in a collecting EDTA (lavender) top tube. The tube is labeled with the name and the birth date of the child and stored at room temperature. A TEDDY Staff Member is visiting the hospitals 3 times a week and collecting the samples and the screening questionnaire.
If the baby is already born or the parents chose to wait until after the baby's birth for the testing, the blood can be taken by heel stick.

Procedures for multiple births

1. Blood samples for twins or triplets must be clearly labeled as Baby A, Baby B, or Baby C. It is extremely important to make sure the correct baby identifier is tracked for these births at every step in the screening and consenting process.
2. Each baby must have its own separate Screening Interview Form and consent form filled out. The correct baby identifier (A, B, or C) must be indicated on the forms.
3. If blood samples from a multiple birth are not clearly marked on the tube as Baby A, Baby B, Baby C, etc., the samples must be thrown away.

Processing and Shipment of the Blood Samples:

A lavender-top vacutainer should be kept at room temperature until it can be processed. Once samples are received at the TEDDY Clinical lab, a local ID is assigned to each subject. The appropriate information, from each subject's screening form, is entered into the DCC screening enrollment database and a TEDDY number is assigned. A lab technician will drop cord blood from the EDTA (lavender) top tube on filter paper. The filter paper has 5 printed rings, on 2 of them the blood is dropped. On the filter paper the local ID is assigned. The blood on the filter paper is allowed to dry on the bench for 30-60 min before being sent by mail to the HLA typing laboratory at the University of Turku, Finland.

Samples are tracked through the process of enrolling screening subjects into the local and DCC databases where study IDs are assigned. Then the filter paper is shipped with a specimen tracking form generated from the TEDDY website to the laboratory performing the initial HLA genotyping. Samples on filter paper are sent to the HLA typing laboratory at the University of Turku, Finland.

TEDDY Cord Blood Storage (only completed if the subject's parent(s) have given consent for blood and DNA storage)

1. Aliquot 0.5 ml in 2ml cryovial, stored at 4˚C
2. If storage consent not given, this sample is only kept until HLA results received

Screening Staff Training
All recruiters and staff who will be engaged with study participants and/or handling blood samples for the screening phase of the study will be trained as following:

Basic requirements for all screening recruiters should include:

- IRB certifications
- Blood borne pathogens training
- Standardized TEDDY screening orientation and training (see below)

Standardized TEDDY screening orientation and training
All recruiters/screening staff are given a standardized TEDDY Study training session at the beginning of their employment (described below).

General training session (similar for recruiting the general population and first degree relatives)
This first session is an overall orientation intended to review the major features of the study, the position, and the job procedures. This session lasts about 4-5 hours. The session is usually conducted by the Screening Coordinator, but can be conducted by another trained TEDDY staff member. The orientation covers several key areas:

- Each recruiter is given a notebook of materials. The screening coordinator thoroughly reviews the information and encourages recruiters to ask questions.
  Notebook materials
  - Information on the TEDDY study (international and site specific)
  - Manual of Operations
  - Screening questionnaire
  - Copies of forms: Informed consent, Brochures, FAQs, letter/instructions for the delivering physician, letter/instructions for expectant parents
  - Articles on diabetes
- Discussion of the study structure with emphasis on the role recruiters will have within the study
- Reviewing screening procedures and forms

- Demonstration and role playing of the interview process (script, informed consent and data collection)
- Review of FAQs and discussion about the types of questions, issues, and problems they will encounter
- Processing of blood samples for HLA genotyping and shipment
- Give tour of study facilities and introduce available staff to new recruiters.

Near the end of the training session, the Screening Coordinator will assess if the recruiter(s) are comprehending the information and satisfactorily performing with the patient interviews. If so, they are incorporated into the hospital or clinic's screening schedule, with the first two days serving as didactic on-site training.

Didactic on-site training (multiple days)
This training will be different for recruiting first degree relatives (telephone) or general population (visit).
General population:
Training of recruiters of general population will be done both at the Diabetes Research Institute and for local staff at the hospitals collaborating with TEDDY. At the first day this training is primarily observational for the recruiter, with the Screening Coordinator (or other TEDDY staff member) demonstrating the screening procedures. The recruiter will observe the screening coordinator go step-by-step through all the screening procedures for the day. The coordinator will explain every step in detail and encourage questions throughout the process:

1. Demonstrate where to obtain required paperwork and how to organize paperwork for the days work.
2. Demonstrate daily cord blood assessment and initial data collection procedures.
3. Demonstrate patient interview procedures with actual patients multiple times as recruiter observes. Discuss after each interview issues and questions that come up during the encounter.
4. Give recruiter the opportunity to conduct a patient interview while coordinator observes. Step in and prompt if necessary. Discuss encounter with recruiter after completion. Provide suggestions for improvement, point out important points that were forgotten, and offer compliments as appropriate. Continue steps 3 and 4 until recruiter has a good mastery of procedures.

First degree relatives:
Training of recruiters of first degree relatives will be done at the Diabetes Research Institute. At the first day this training is primarily observational for the recruiter, with the Screening Coordinator (or other TEDDY staff member) demonstrating the screening procedures by telephone/mail. The recruiter will observe the screening coordinator go step-by-step through all the screening procedures. The coordinator will explain every step in detail and encourage questions throughout the process:

1. Demonstrate where to obtain required paperwork and how to send materials and the cord blood kit to families.

2. Demonstrate daily cord blood assessment and initial data collection procedures.
3. Demonstrate patient interview procedures by telephone with actual patients multiple times as recruiter observes. Discuss after each interview issues and questions that come up during the encounter.
4. Give recruiter the opportunity to conduct a patient interview by telephone while coordinator observes. Step in and prompt if necessary. Discuss encounter with recruiter after completion. Provide suggestions for improvement, point out important points that were forgotten, and offer compliments as appropriate. Continue steps 3 and 4 until recruiter has a good mastery of procedures.

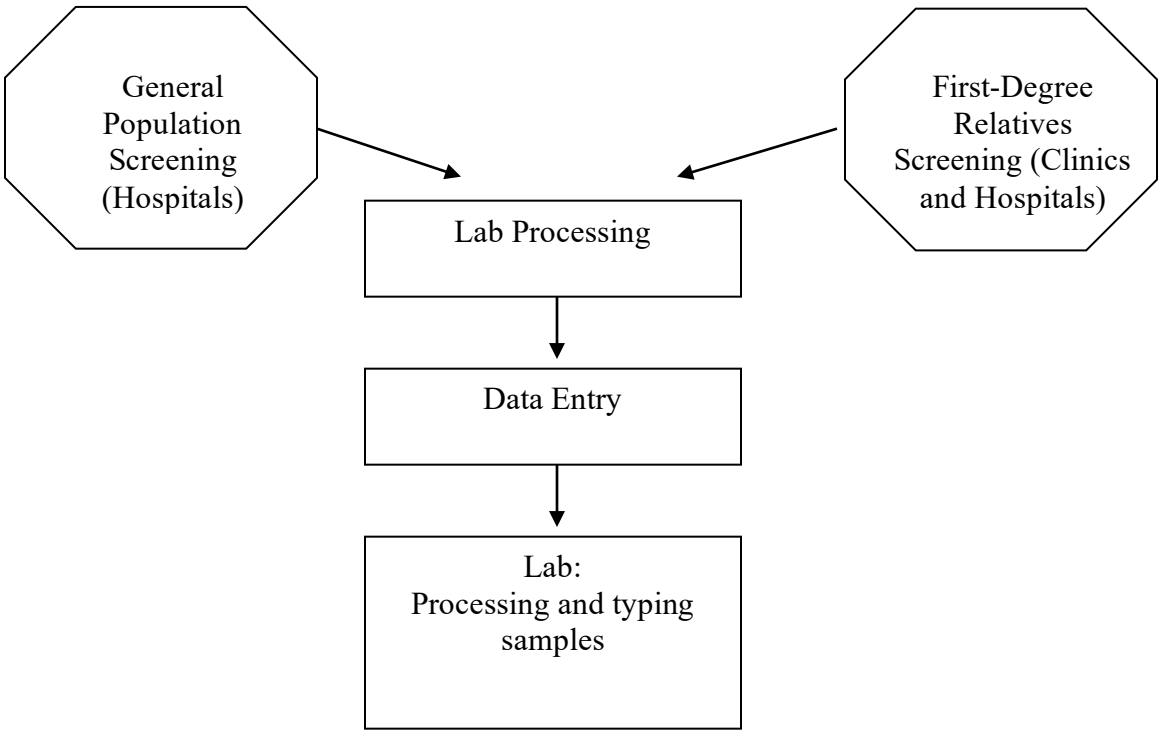
FOLLOW-UP SUPPORT: The Screening Coordinator remains available via phone and email for the recruiters after formal training has been completed. Recruiters are encouraged to contact the coordinator with questions or for clarification.
One screening per quarter with group/individual will be certified/observed by the Screening Coordinator.
Quarterly meetings are planned with recruiters to review emerging issues, protocol questions, quality control debriefs.

A4. Site Specific Screening Procedures: Georgia/Florida

Table of contents:

Screening Plan Overview

Flow chart of Georgia/Florida screening process



Purpose: To identify newborn children with elevated risk for T1DM based on HLA genetic markers from the general populations of newborns and among newborns with a first degree relative with T1DM.

Each institution participating in TEDDY through the GA/FL clinical site is responsible for screening a portion of newborns during the study's four-year screening period. A proportion of those screened will be identified as having the higher risk genes and will therefore be eligible for participation in the prospective follow up. The approach to screening varies between the institutions.

TEDDY screening began October 1, 2004 and will last for 4 years. The anticipated rate of screening enrollment and identification of eligible subjects is as follows:

- Total screened from all GA/FL sites combined: 12,000/year, 150 of which will have an affected FDR
- Total eligible from all GA/FL sites combined: 660/year, 45 of which will have an affected FDR

Screening sites:

- Medical College of Georgia, Augusta, GA
- University Hospital, Augusta, GA
- St. Joseph Hospital, Augusta, GA
- Northside Hospital, Atlanta, GA
- Shands Teaching Hospital (UF), Gainesville, FL
- Shands at AGH, Gainesville, FL
- North Florida Regional Medical Center, Gainesville, FL

Screening Eligibility Criteria: General Population & FDR

Infants are eligible for screening if they:

- Are less than 4 months of age.
- Have a parent or primary caretaker age 18 or older who has given informed consent for screening.

Additional FDR-specific eligibility criteria:
Initial eligibility for the FDR cohort requires that the infant has a first degree relative with type 1 diabetes. This includes biological mother, father, or sibling. A biologically related half sibling alone does not meet this criterion. An infant whose only relative with type 1 is a half sibling would qualify for the general population cohort screening.

Infants are excluded from screening if they:

- Have an illness or birth defect that precludes initial screening (baby is in NICU or special care nursery)
- Have an illness or birth defect that precludes long-term follow-up or involves use of treatment that may alter the natural history of diabetes (e.g. steroids or insulin).

Screening Procedures

Screening activities across all sites include the following elements:

1. Screening interview, providing materials to parents and answering questions.
2. Obtaining informed consent
3. Collection and transfer of the blood sample to the lab for HLA typing
4. Logging blood samples
5. Data entry to local TEDDY database
6. Registering participants with the DCC

1. **Screening interview, providing materials to parents and answering questions**

A. Approaching Potential Participants (Moms)

Each site will have a specific procedure for who approaches potential participants (TEDDY staff or authorized representatives) for screening, and at what time point (in labor, or 12-24 hours post-partum). The details for each site will be tailored for that site's work flow and approved by their IRB. Some sites will collect cord blood samples on all babies born, and the mothers will be approached about TEDDY screening 12-24 hours post-partum. Other sites will collect blood spot sample through heel sticks done in conjunction with the state-mandated PKU once informed consent is obtained, either during labor or post-partum. The TEDDY office responsible for each site will ensure that the site is supplied with all necessary screening materials, such as Newborn Screening Forms, Informed Consent documents, brochures or other information documents, blood spot sample collection forms, and any other materials such as pens, clipboards, stickers, etc. TEDDY staff will also be responsible for collecting and matching all signed informed consents to each completed blood spot sample collection forms and transporting them to the TEDDY office.

B. Completing the Newborn Screening Form

Subject contact information will be collected on a Newborn Screening Form and entered into the local TEDDY database. The data that is uploaded to the DCC database will be stripped of identifiers.

C. Brochures and Materials Left with Consenting Subjects

The TEDDY screening brochure is given to the potential subject's mom along with the consent document. The TEDDY representative will review the materials with the mom and invite her and others family members present to ask questions as they consider participating in the screening.

2. Obtaining informed consent

A signed informed consent will be obtained for every study participant. The screening location and method used to obtain the informed consents will vary by TEDDY site, and will be approved for that site by their own IRB. All elements of the informed consent document that are required will be completed, including signatures, dates, initials, etc. It is the responsibility of the TEDDY office in charge of that site to be sure all collected consents are completed according to the requirements of the site's IRB.

3. Collection and transfer of the blood sample to the lab for HLA typing

HOSPITALS – GENERAL POPULATION SCREENING PROCEDURES

Cord Blood Samples

Cord blood collection upon delivery

Cord blood samples are routinely collected on all newborns at certain TEDDY sites. In the cases where cord blood is collected, the labor and delivery staff will place cord blood samples on the

blood spot collection forms (provided by the TEDDY office) and complete at least the minimum amount of identification information for the mother and child on the form. Those sites will leave the blood sample forms for the TEDDY staff to collect in the location they designate. Once TEDDY staff has obtained a signed informed consent document for the subject, the subject's sample can be released to TEDDY personnel.

If cord blood samples are missed during delivery, they can usually be obtained by the nursery staff responsible for obtaining the state PKU (see section below). TEDDY staff will communicate with nursing staff regarding which subjects need samples obtained with the PKU, and will be responsible for retrieving the completed sample cards and matching them to signed informed consent documents.

Heel Stick Samples

Capillary blood collection in conjunction with PKU

Blood samples for genetic screening are obtained through a heel stick in conjunction with the PKU sample collection at several TEDDY sites. In these cases, the nursing staff responsible for collecting the PKU will also collect the TEDDY sample at the same time. TEDDY blood spot collection forms will be provided by the TEDDY staff, and placed in the baby's chart along with the PKU form, or in the location specified by the institution. The nursing staff that collects the blood spot samples will leave the cards to dry in a location designated by the institution for collection by TEDDY staff. All completed blood spot forms will be matched to a signed informed consent for the subject before the subject is registered in the local TEDDY database and before any laboratory tests on the sample are begun.

Signed consent with no sample

In the case where a mother has been interviewed about participation in the study and has agreed and signed a consent form, but the sample was missed either at delivery or with the PKU or both, we will pursue collecting that sample for a limited amount of time. Once it is determined that sample on a willing subject has been missed, TEDDY staff will contact the family to inform them of the situation and ask if they are still willing to have the baby screened. If the answer is no, the informed consent will be destroyed. No record of the subject will be recorded in the local TEDDY database. If the answer is yes, TEDDY staff will try to find a way that is most convenient and practical for the family. The family will have the choice of bringing the baby into the TEDDY office to have TEDDY staff perform the heel stick, or allowing TEDDY staff to work with their health care provider to obtain a heel stick sample through them during a visit. This effort to obtain a sample will continue for no more than 2 weeks after the baby is born to allow for enough time to determine eligibility for follow-up and schedule and complete a first visit.

Sample with no signed consent

In the case where a sample has been collected on a baby, and the family has agreed to the screening, but the consent form is not complete, TEDDY staff will pursue a completed consent for a limited period of time. As stated above, no subject information will be entered into the local TEDDY database, and no laboratory tests will be performed on the sample until a completed informed consent is obtained. TEDDY staff must inform the family of the situation

and may work with the family to complete the consent for up to two weeks after the baby's date of birth.

INTERVIEW PROCEDURE

1. Gather the paperwork and organize by the order in which you will visit the rooms.

IMPORTANT: Prioritize mothers to be interviewed by whether they are going home that day or not. These mothers should be interviewed first.

2. Knock on door and ask if you can enter room. If the mother is busy with family or hospital care staff, sleeping or not in her room, make a note of this, and return later, if you can. If mother is present, introduce yourself and explain that you are from the TEDDY study, clearly stating that you are there to tell them about a research study that is optional for their baby. Briefly explain study and the newborn genetic screening. Ask if they want to participate, and encourage the family to ask questions.

    - **NOTE**: *At least one of the newborn's parents must speak fluent English in order to complete the consent process. This parent who speaks English must be the one consented as the primary caretaker of the newborn for purposes of the study. The Recruiter cannot allow a family member to translate the consent form for the non-English speaking parent. This is not considered a true informed consent. Capabilities to screen Spanish-speaking families will be implemented in the future.*

If family wants to participate:

- Help them complete the informed consent with all necessary signatures, dates, initials, etc.
- Give the family a copy of the consent to keep for their records, along with the TEDDY screening brochure containing our contact information.
- Complete a newborn screening form, ensure legibility
- Offer to answer any questions they have, and encourage them to call the office if they think of any questions later
- Tell them they can expect a letter regarding results in 4 to 6 weeks
- Congratulate and thank the family as you leave

If family does NOT want to participate:

- See if you can gently encourage participation by asking appropriate questions or supplying additional information. Examples: (1) Most children (85 to 90%) who develop type 1 diabetes do not have a family member with type 1, so we feel that testing each child is very important. (2) The test is free of charge and confidential. (3) The sample has already been taken or will be taken at the same time as the PKU, so there are no additional sticks to the baby.
- If they still do not want to participate, leave them a copy of the brochure and let them know they can contact us, and can still have the baby screened before 2 months of age if they change their minds.
- Congratulate and thank the family as you leave

POST INTERVIEW PROCEDURE

1. Once all the interviews are completed, organize the paperwork. Check to make sure all screening forms are filled out completely, that every consent and screening form is signed, dated, legible, etc.

2. For those who consented to screening, make sure a sample either 1) has been collected at delivery or 2) will be collected with the PKU according to the procedures for that site.

3. For samples to be collected with the PKU: complete at least the minimum information on the blood spot collection form (mother's first and last name, baby's last name, baby's date of birth, baby's sex). Place the form in the appropriate location to alert the nursing staff that the sample is to be drawn along with the PKU.

4. Collect all samples ready for pickup and match to the screening form and signed consent for that subject.

CLINICS – FIRST-DEGREE RELATIVES SCREENING PROCEDURES

To meet First Degree Relative (FDR) screening and recruitment goals, the Georgia/Florida sites will partner with health professionals working directly with people with T1DM to identify newborns eligible for TEDDY screening. The term "clinics" will refer to all medical settings providing care to patients, including hospital clinics and independent practices. Screening strategies will vary, based upon the structure of each health setting. The TEDDY office nearest each clinic site will provide all recruitment/enrollment materials for the clinic, such as brochures, posters, screening forms, informed consent and assent documents, etc. Clinics will include, but are not limited to, the following:

	Target Audience	
	Adults with T1DM expecting a baby or have a newborn < 4 months	Parents of a child with T1DM, and are expecting another baby or have a newborn < 4 months of age.
Diabetes Clinics	X	X
Adult Endocrinology Clinics	X	
Pediatric Endocrinology Clinics		X
OB/GYN Clinics	X	

FDR Eligibility Criteria Questions:

The following questions will be used to identify FDR newborns (offspring or full sibling) who would be eligible for TEDDY Study screening:

Diabetes Clinics:

- Is patient expecting a baby? (*question applies to men and women*)
- Does patient have child less than 4 months old?
- Is a parent of a child patient expecting a baby?
- Does patient have a brother/sister less than 4 months old?

Adult Endocrinology Clinics:

- Does patient have child less than 4 months old?
- Is patient expecting a baby? (*question applies to men and women*)

Pediatric Endocrinology Clinics:

- Does patient have a brother/sister less than 4 months old?
- Are patient's parents expecting a baby?

OB/GYN Clinics:

- Does expectant mother or biologic father have T1DM?
- Does expectant mother have another child with T1DM?

FDR Genetic Screening Procedures

- Self-referred – some patients will approach us upon hearing about the study through the clinics or other means. At that point, we will proceed with getting them set up with enrollment materials through the nearest TEDDY office.

- Approached by TEDDY – some patients will be approached by TEDDY staff directly or by designated representatives of TEDDY, usually their health care providers, about participation in TEDDY. All personnel obtaining informed consent for TEDDY will be trained by a TEDDY office supervisor or PI, and will be recorded on the TEDDY Consentor list in the regulatory documents binder.

Recruitment Tracking

The recruiter will keep a log book and/or Excel file to record the patients who are expecting and their due dates, the patients who are contemplating participation, patients who have declined participation, and the names of patients who may have interest in the future (i.e. Pregnancy Status List).

HLA typing: Blood Sample Storage, Transfer and Shipment

Blood Sample Collection

1. Most TEDDY sites conducting newborn screening will rely on the site's nursing staff to collect blood stick samples via heel stick in conjunction with the PKU or from the umbilical cord during delivery. All blood samples regardless of method collected will be placed on filter paper collection forms as blood spots. Blood spot samples will be allowed to dry at room temperature overnight or until completely dry before they are removed form the collection site by TEDDY staff.
2. If a TEDDY staff member recruits an infant younger than 3 months into the study for genetic screening and collects the blood sample him/herself, it will be collected by heel stick using the following procedure:

Equipment

a. 70% isopropyl alcohol prep wipes
b. Gauze
c. Sterile lancet (Quikheel ™ or Tenderfoot ™ are commonly used
d. Heel warming device
e. Filter paper collection forms

Process

1. Apply a warming device to the infant's heel approximately 3 minutes before the skin puncture to increase the blood flow.
2. The site to be used for the heel stick should be pink or normal color, and free of scars, cuts, bruises, or rashes. Do not choose a site that is cyanotic (bluish in color) or edematous (swollen).
3. Clean the site with an alcohol wipe. The site should be completely dry before the skin puncture.
4. Open the sterile lancet and remove from packaging right before puncture. Don gloves before grasping the foot in a firm but gentle hold by wrapping fingers around the bottom of the heel and around the top of the foot.
5. Position the lancet device on the site firmly applying gentle pressure, this assists in decreasing the sensation and ensures the puncture depth is adequate. Puncture the heel on the sole of the foot with the Quickheel lancet device, dispose of the device in a sharps container.
6. Apply gentle pressure to the site while wiping away the first drop of blood on a dry piece of gauze.
7. Position the infant's foot downward to enhance blood flow and continue to apply gentle pressure to the tissue surrounding the heel puncture site
8. Collect the blood on appropriate the blood spot collection form. Be sure the circles are filled completely, and soaked through to the other side of the paper.
9. Once collection is complete, apply pressure to the heel site with clean gauze until bleeding stops, then apply bandage.
10. Label the specimens per Lab Protocol, dispose of contaminated materials in the sharps box, throw away opened materials not used, remove gloves, and wash hands. Allow sample to dry at room temperature.

4. Logging Blood Samples

Each blood spot sample collected should have enough identifying information on it to link the subject to the signed informed consent and screening form. Once the written information is complete, the spot forms will also receive a specimen ID in the form of a numbered sticker. The stickers are printed in quadruplicate, and are placed like this:

1) 1 sticker is applied to the detachable filter paper end of the blood spot form.
2) 1 sticker is applied to the larger, text area of the blood spot form.
3) 1 sticker is applied to the screening form
4) 1 sticker is applied to the outside flap of the blood spot form storage envelope.

The specimen IDs for TEDDYsubjects are generated as sequential numbers in an Excel file. The subject's name and appropriate information is recorded in the Excel file, and copies of the logged subjects are printed and stored in a binder as hard copies to back up the TEDDY database. The subject's original consent and screening form are stored in files at the nearest TEDDY office, filed by specimen ID.

The stickered blood spot cards are transferred to the CBGM HLA lab on the MCG campus once they have been logged into the binder and database. The laboratory technicians then punch

aliquots of the spot samples into master plates for HLA typing. The original spot card is stored at room temperature in a locked, dry location, filed according to specimen ID.

5. Data Entry to local TEDDY database

TEDDY subjects and their specimens are loaded into the local TEDDY database on a daily or as needed basis. Please refer to the TEDDY database manual for detailed instructions on how to enter/enroll TEDDY subjects.

6. Registering participants with the DCC

TEDDY subjects also need to be registered with the DCC after they are enrolled and entered into the local TEDDY database. The process is an automated transfer of data from the local TEDDY database to the DCC database. The details of this data transfer are available in the TEDDY user manual. What follows is a brief overview:

Submitting Screening Form Data

1. From GEO local TEDDY database system, get a report regularly (weekly to bi-weekly) on a list of enrolled newborn subjects who need to be submitted to DCC.
2. Generate an XML Screening Form file from the report.
3. Log into DCC's TEDDY website, upload the Screening Form XML file.
4. DCC processes the Screening Form XML file from GEO, assigning a Subject ID for each subject, then DCC emails a returned XML file that reports the import status of each enrolled newborn subjects.
5. From the returned XML file, GEO local TEDDY database imports DCC-assigned Subject ID and status into local database.

Submitting HLA Results Data

1. From GEO local TEDDY database system, get a report regularly (weekly to bi-weekly) on a list of HLA results data for enrolled newborn subjects.
2. Generate an HLA Results Data file on MS Excel format.
3. Log into DCC's TEDDY website, upload the HLA Results Data file.
4. DCC processes the HLA Results Data file and send back a returned file that reports the import status of each HLA results data.
5. From the returned file, GEO local TEDDY database imports the status into local database.

TEDDY Staff Training

Training of recruiters and other staff for screening procedures will vary across clinical sites, as well as across the cohorts being screened. Recruiters must fulfill the mandatory training requirements set forth by the institutions where they will be working or affiliated. Across all clinical sites, however, a minimum level of certification and training should be met by all recruiters and staff who will be engaged with study participants and/or handling blood samples for the screening phase of the study.

Basic requirements for all screening recruiters should include:

- IRB and HIPAA certifications
- Blood borne pathogens training
- Phlebotomy (if drawing blood from participants)
- Standardized TEDDY screening orientation and training (see below)

Standardized TEDDY screening orientation and training

Each coordinating office for the Georgia/Florida center should include these same basic features as part of training and orientation for recruiters.

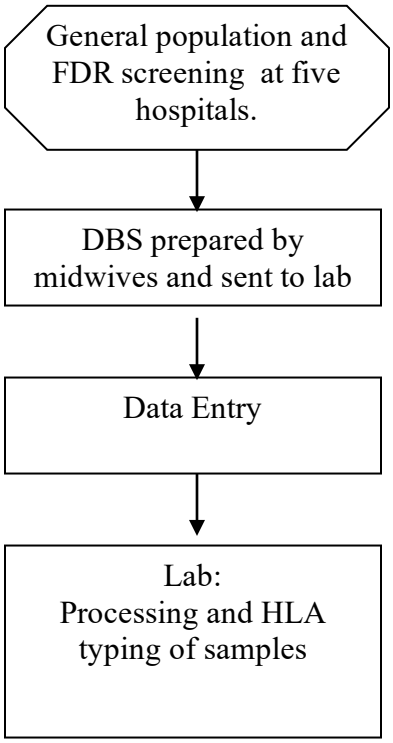
- Provide overview of TEDDY Study (international and site specific).
- Review and explanation of TEDDY MOO. Emphasis placed on site specific screening process MOO.
- Detailed review of data collection forms and description of reason/need for each field.
- Role-play participant interview and informed consent.
- Conduct observational and quality control on-the-job training (recruiter observes how interview should be conducted and then supervisor observes recruiter conduct interview multiple times to assess and ensure mastery of the protocol).
- Demonstrate and have recruiter practice every step of the blood collection process until mastered by recruiter.
- Give tour of clinic, lab, hospital, etc and introduce recruiter to staff.
- Provide informational articles on diabetes and study's FAQs.

FOLLOW-UP SUPPORT: The Screening Coordinator remains available via phone and email for the recruiters after formal training has been completed. Recruiters are encouraged to contact the coordinator with questions or for clarification. Experience has shown us that the more support you can provide recruiters in the first two months in their duties, the more self-sufficient and confident they will be.

A5. Site Specific Screening Procedures: Sweden

Screening Plan Overview

Flow chart of Sweden screening process



Purpose: To identify newborn children with elevated risk for T1DM based on HLA genetic markers from the general populations of newborns and among newborns with a first degree relative with T1DM.

Consent

A brochure offering information about TEDDY is given to all pregnant mothers at their visit to a Maternal Health Care Clinic in the Region Skåne. The brochure is produced in Swedish only.

There are more than >100 Maternal Health Care Clinics in Skåne in addition to Specialist Health Care Clinics for mothers with diabetes and other diseases. In addition, there are some private Maternity Health Care Clinics, which have also been provided with the TEDDY information material. The midwives also offer verbal information about the study to the parents. Posters about TEDDY are displayed in the clinics and a video about childhood diabetes is shown to the mothers. The midwives who operate the Maternal Health Care Clinics are informed twice a year by TEDDY study personnel (Study coordinator and Lead Research Nurse) at clinic conferences. The midwives are also informed about the procedure to collect cord blood as Dried Blood Spots. This ensures that

study information also reaches parents prior to being approached to participate in the TEDDY screening.
Consequently the initial subject contact is made by the midwife at the Maternal Health Care Clinics. This procedures ensures that almost all pregnant mothers are informed about the TEDDY study and about childhood diabetes.

At the time of delivery, the midwife will obtain an oral consent from the mother and the father to participate in the screening part of the TEDDY study.
The consent is obtained at the time the mother is registered at the Maternity Clinic.
The Region Skåne has five Maternity Clinics:

Förlossningsavdelningen
Lasarettet
251 87 Helsingborg

Förlossningsavdelningen
Centralsjukhuset
291 85 Kristianstad

Kvinnokliniken, förlossningsavdelning
Universitetssjukhuset i Lund USIL
221 85 Lund

Förlossningsavdelningen
Kvinnokliniken
Universitetssjukhuset MAS
205 02 Malmö

Ystad BB
Lasarettet
271 82 Ystad

After consent is given, the midwife will collect blood from the umbilical cord after delivery. The cord blood is withdrawn with a syringe inserted into the cord to collect as much blood (1-15 ml) as possible. The midwife or her assistant will drop blood onto the six rings to prepare Dried Blood Spots (DBS) on the TEDDY Screening Remittance. The TEDDY Screening Remittance has the local subject ID number printed on it.

Mothers who change their minds about participating can say “no” after delivery as well. In this event the TEDDY Screening remittance will be destroyed and no records of the non-consenting mother will be made.

The TEDDY Screening remittance is left on the bench to dry at room temperature for no more than 2 hours. The filter is next placed in a TEDDY Transport Box. This box is picked up by Region Skåne Mail personnel and taken for HLA typing to the TEDDY Laboratory at the Wallenberg laboratory at the University Hospital MAS in Malmö. The

transportation of TEDDY Screening Remittances will take place each work day and delivered at the TEDDY Laboratory before 1.00 PM Monday-Friday.

Collection
The TEDDY Screening Remittance is received on working days at TEDDY Laboratory for HLA typing. The Remittance is put into a plastic cover to keep it free from dust and moist and then kept at room temperature in binders unique to each city of delivery. The information on the Remittance is entered into the TEDDY DCC Registration form.

Processing
Punch-outs being 3 mm in diameter are obtained in a Wallac Automated Puncher and directly distributed into 96-well micro titer plates. Spots for 90 participants are punched into individual wells in each plate. The remaining wells are left empty for control samples. Triplicate samples are needed for each participant, but each of these spots should be punched into a separate plate resulting in three identical plates containing samples from the same 90 participants. Punch three blank filter paper spots (not to be punched into the plate) between each actual blood spot punch in order to avoid contamination.

Local Lab Processing and PCR
When the plate is completed it is ready to PCR. The Perkin Elmer Wallac method is used for HLA typing as detailed in the instructions from the company.

Storage of dried blood spot filters.

Each filter is inserted into a plastic cover and stored in binder at room temperature. After completion of the HLA typing the filters are kept at room temperature and in the dark in locked fire secure cabinets.

A6. Site Specific Screening Procedures: Washington

Consent

The blood sample will be collected as an unused portion of the Newborn Screening Program (NSP) sample. A TEDDY brochure offering a free genetic risk screening (accomplished at the same time as the Newborn Screening materials) is included in the standard New Mother Packets delivered to all obstetrics patients at their doctor's office for their third trimester visit and upon admittance to the hospital. This ensures that study information reaches parents prior to being approached by TEDDY staff.

Initial subject contact is made by the hospital nursing staff to determine if the potential subject is interested and willing to talk with one of the researchers (see "Hospital Script" attached). TEDDY Staff visit the hospitals twice daily and check with the nursing staff to determine which mothers are comfortable post partum and interested in discussing the study. No families are approached by TEDDY staff less than 8 hours after delivery. The researcher explains in detail the screening and follow-up portions of the study and obtains consent from interested families. If the new parents would like additional time to consider participation they are given the option to take all of the forms home. TEDDY staff follow-up with these families by phone in one week to determine interest (see "Hospital Callback Script" attached).

If the consent form is signed at the hospital, the afternoon screener places a "TEDDY" sticker on the Newborn Screening card at the end of Screening shift. NSP cards are kept in the Dynacare lab after collection and are available for labeling anytime after 2:00 pm each day until they are sent to the NSP Office the next morning at 9:00 am. If a Newborn Screening card is not available for a consented subject, note the name and date of birth of the subject and communicate this information to the TEDDY screener on duty for the next afternoon shift. These cards are labeled with a "TEDDY" sticker if the cards become available at the end of the shift.

If consent is obtained by phone, after the family has returned home, a signed consent form must be mailed to the Clinical Center prior to sample collection at NSP. Those families who give oral consent are instructed to send the study consent form to the Clinical Center immediately. When the consent form arrives, one of the researchers contacts NSP to have the child's card labeled with a " TEDDY" sticker and set aside with the other cards labeled with" TEDDY" stickers.

Collection

Triplicate 1/8-inch punches are requested from NSP in order to avoid any need for future re-punching of samples that do not amplify. Before a sample can be released to TEDDY, a copy of each participant's signed consent form must be given to NSP. TEDDY personnel deliver copied consent forms to NSP and work with their staff to pull the individual cards and to punch the spots at the NSP labs. Blood spot cards are available at NSP one week after the sample is taken at the hospital. Therefore, TEDDY staff go to the NSP offices twice a week to deliver the new consent forms and pull and punch blood spots from all of the screening cards marked "yes". Cards should be punched for

TEDDY within two weeks of arrival at NSP. Cards that do not have a "yes" sticker are considered a negative consent, and TEDDY personnel do not handle those cards.

Processing

The dried blood spot samples are punched into 96-well microtiter plates. Spots for 90 participants are punched into individual wells in each plate. The remaining wells must be left empty for control samples. Triplicate samples are needed for each participant, but each of these spots should be punched into a separate plate resulting in three identical plates containing samples from the same 90 participants. Punch three blank filter paper spots (not to be punched into the plate) between each actual blood spot punch in order to avoid contamination. Cover each microtiter plate, label it with the plate number and the date, and secure it with a rubber band. The following method is used to name the identical triplicate plates: T-1a, T-1b, and T-1c. The next set begins T-2a and so on.

Storage and Shipment to Local Lab

At the end of the pull/punch shift at NSP, TEDDY staff transport filled plates with computer generated plate maps to the lab at PNRI for genotyping. The sample will be analyzed for HLA genotypes to determine if the child's genotype meets inclusion criteria for the Surveillance part of the study.

Local Lab Processing

When the plate arrives at the lab, the following steps must occur before it is ready to PCR.

When the plates are received:

1) Carefully take lids off plates – spots may jump so be extremely careful
2) Record any samples that have jumped out of the assigned wells or wells that have multiple spots in them
3) Also record samples that are only white filter paper punches
4) Methanol fix the samples
5) Add 100uL of J. Baker Methanol to each well using a multichannel (repeater will cause DBS to jump and possibly contaminating other wells)
6) Let the plates dry uncovered for 48-72 hours
7) After plates are completely dry and no methanol can be detected, cover plates with a lid and label with plate name and date plates were methanol fixed.
8) Place plates in a closed container with desiccant until ready to PCR.

When ready to PCR:

The samples must be transferred from the 96-well microtiter plates to a 96-well PCR plate.

1) Observe the position of the A1 well of the PCR plate and the H1 well of the microtiter plate.
2) Flip the microtiter plate onto the PCR plate aligning the A1 well of the PCR plate with the H1 well of the microtiter plate.
3) The samples are ready to PCR.

B. MODEL SCREENING INFORMED CONSENTS

IRB#

Informed Consent to Participate in Research and Authorization for Collection, Use, and Disclosure of Protected Health Information

You are being asked to take part in a research study. This form provides you with information about the study and seeks your authorization for the collection, use, and share and disclosure of your Protected Health Information necessary for the study. The Principal Investigator (the person in charge of this research) or a representative of the Principal Investigator will also describe this study to you and answer all of your questions. Before you decide whether or not to take part, read the information below and ask questions about anything you do not understand. Your participation is entirely voluntary.

a. **1..... Name of Participant ("Study Subject")**

_____

2. Title of Research Study

The Environmental Determinants of Diabetes in the Young (TEDDY) Study
Part 1: Screening

3. Principal Investigator and Telephone Number(s)

Co-Principal Investigator(s):

Co-Investigator(s):

Research Coordinator:

Research Nurses:

4. Source of Funding or Other Material Support

National Institutes of Health, USA

5. What is the purpose of this research study?

Your child is being asked to join a study to help determine what causes type 1 diabetes mellitus (T1DM). T1DM used to be called childhood diabetes or insulin-dependent diabetes. T1DM occurs when special cells in the body, called the beta cells of the pancreas, are destroyed by the body's infection fighting cells, called immune cells. Evidence that these cells are being destroyed is seen by the presence of antibodies against the beta cells in the blood called autoantibodies. When these beta cells are completely destroyed, the body cannot make the chemical insulin. Insulin is needed for the body to use food. Insulin helps keep the sugar level in the blood normal. If there is no insulin in the body, the sugar in

the blood becomes high and this makes someone get sick. When a child develops T1DM, they must take insulin by shots or pumps every day to stay well.

Research tells us that children who get diabetes have certain kind of genes. Other children who have these genes are at higher risk for getting diabetes. However, not all children who are higher risk get diabetes. We think that something happens that "triggers" or causes a child with higher risk genes to actually get diabetes. It is the purpose of this study to try and find out what are the triggers that cause children to get diabetes.

This study will look for children with this high-risk gene. Most children do not have higher risk genes for T1DM. In the next phase of this study we hope to determine possible environmental factors that may cause T1DM.

We will have to study over 220,000 children to find enough with higher risk genes. To find enough children, six places around the world have agreed to do this study.

6. What will be done if you take part in this research study?

You are being asked to allow your baby to take part in this research study. We will take a tube of blood from the cord that is thrown out after the baby is born. Or, we will stick your baby's heel or finger to get 2-3 drops of blood. The law requires newborn's blood to be tested for certain diseases. We will get our blood at the same time so the baby does not have to be stuck twice.

What will be done with your child's blood? Your child's blood will be sent to a laboratory. The laboratory will test the blood to see if your baby has a certain kind of gene. We are looking for babies who have higher risk genes for T1DM.

If your baby does not have higher risk genes for T1DM, we will tell you in a letter and your baby's blood sample will be destroyed. If your baby does have higher risk genes, we will call you within 12 weeks. Your baby could then be enrolled, with your separate consent, in the second part of our research study. We will follow babies with higher risk genes to see why some babies get T1DM and others do not. We will be looking for possible environmental factors leading to autoantibodies or the development of T1DM.

7. What are the possible discomforts and risks?

If we get blood from the cord, your baby will feel nothing. If the blood comes from a heelstick or a finger stick, the baby may cry. There could be a bruise or swelling or infection. The risk of infection is small.

If your child has higher risk genes for T1DM, you may feel worried or stressed. Some people worry that a person with higher risk genes might be denied health insurance or life insurance. To protect your baby, we will not tell anyone else about your baby's genes. We will keep your baby's genetic information in locked files. Your baby will be given a number so names will not be used. Only members of the TEDDY study team will be able to use the locked files.

No information will be put in your child's medical record by the study personnel. You may want to talk about the study with your child's physician. However, we suggest study information not be placed in your child's medical record.

We want to answer all of your questions. We are here to answer your questions today. Later, you may think of other questions. Please call the Principal Investigator ……..or the Coordinator…….. or …….**(Site specific)** if there is anything you want to discuss.

8a. What are the possible benefits to you?

If your baby has higher risk genes for T1DM, your baby could be followed in Part 2 of the study. We would also tell you any new information we learn about what causes T1DM. We would tell you about any studies to prevent diabetes that might be right for your child. If your child got T1DM, we might find it quicker, before your child gets very sick. We would tell you about any studies for children with newly diagnosed T1DM.

8b. What are the possible benefits to others?

The results of this study will help us understand why some children with higher risk genes get T1DM while other children with the same gene do not. When we understand this, we can try to prevent the disease.

9. If you choose to take part in this research study, will it cost you anything?

No.

10. Will you receive compensation for taking part in this research study?

You will not be paid for taking part in this study.

11. What if you are injured because of the study?

If your child is injured by a study procedure, only professional medical care that you receive at …… will be provided without charge. Hospital expenses will have to be paid by you or your insurance provider. **(Site specific)**

12. What other options or treatments are available if you do not want to be in this study?

You are free not to participate in this study. If you choose to participate, you are free to

withdraw your consent and drop out at any time without this decision affecting your medical care.

13a. Can you withdraw from this research study?

You can drop out of this study at any time. There are no penalties for dropping out. You will not lose any benefits you are entitled to.

If you decide to drop out, you should contact ……..…..at…….…… .

If you have any questions regarding your rights as a research subject, you may phone the Institutional Review Board (IRB) office at……...

13b. If you withdraw, can information about you still be used and/or collected?

If you drop out of the study, we will not collect any more information from you or your child, unless you allow us to contact you annually to ask a few questions about the health of your child. Information we got before you dropped out may be used, but your child's name will never be used.

13c. Can the Principal Investigator withdraw you from this research study?

You may be taken out of the study if you do not meet the study requirements. You may be taken out if the TEDDY study team thinks the study would do you or your child harm. The National Institutes of Health is paying for the study. It can stop the study at any time.

14. How will your privacy and the confidentiality of your Protected Health Information be protected?

Your child's health records are considered protected health information. These health records can include your child's family history of T1DM and your child's genetic test results. Only members of the TEDDY study team and the Institutional Review Board have the legal right to see your research records. We will not show your research records to anyone without your permission.

When we talk about the study at scientific meetings, we will never use your name or your child's name. When we write about the study in scientific journals, we will never use your name or your child's name.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will

use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Even with the Certificate of Confidentiality, the investigators continue to have ethical and legal obligations to report child abuse or neglect and to prevent you from carrying out any threats to do serious harm to yourself or others. If keeping information private would immediately put you or someone else in danger, the investigators would release information to protect you or another person.

DHHS personnel may request identifying information for purposes of performing audits, carrying out investigations of DHHS grant recipients, or evaluating DHHS funded research projects.

15. If you agree to participate in this research study, what Protected Health Information about you may be collected, used and disclosed (given) to others?

As part of this study, some of your child's health information will be collected, used, and shared with the TEDDY study team. This information is considered protected health information and includes your child's family history of T1DM and your child's genetic test results.

16. For what study-related purposes will your Protected Health Information be collected, used and shared?

The study will try and find out why some children with the high-risk gene get T1DM and other children do not. To answer this question, we need to find children with higher risk genes for T1DM.

17. Who will be authorized to collect, use and disclose to others your Protected Health Information?

Members of the TEDDY study team may collect, use, and share among themselves your Protected Health Information.

18. Once collected or used, who may your Protected Health Information be disclosed to?

Your Protected Health Information may be given to:

- the National Institutes of Health which is paying for the study
- Government agencies responsible for overseeing research. These agencies may include the Food and Drug Administration, the Department of Health and Human Services, and the Office of Human Research Protections
- Government agencies responsible for overseeing public health. These agencies may include the Centers for Disease Control and Federal, State and local health departments
- Institutional Review Board
- TEDDY researchers

19. If you agree to participate in this research, how long will your Protected Health Information be collected, used and disclosed?

Your Protected Health Information could be used or shared for many, many years. Right now, we do not know when the study will end.

20. Why are you being asked to authorize the collection, use and disclosure to others of your Protected Health Information?

Under a new US Federal Law, researchers cannot collect, use or share your Protected Health Information without your permission.

21. Are you required to sign this consent and give your permission for researchers to collect, use and share your Protected Health Information?

No. You do not have to agree to be in this study. If you do not want to be in this study, it will not affect your medical care or your child's medical care.

If you want to be in the study, you must sign this consent form. You must also give your permission for the TEDDY study team to collect, use and share your Protected Health Information.

22. Can you review or copy your Protected Health Information collected used or disclosed under this authorization?

Every five years and at the end of the study, you can see or copy your Protected Health Information.

23. Is there a risk that your Protected Health Information could be given to others beyond your authorization?

We will do our best to protect your health information. We will give it only to the TEDDY study team, the Institutional Review Board, and the groups listed in item 18 above. However, it is possible that someone else could see your Protected Health Information. This may happen if you share this information with you regular health providers and the information is placed in you medical records.

24. Can you revoke (cancel) your authorization for collection, use and disclosure of your Protected Health Information?

Yes. You can drop out of the study at any time. If you drop out, no new information will be collected about you or your child. However, information we got before you dropped out may be used and shared. If you do not want us to use or share that information, you must say that in writing. Send your written request to the Principal Investigator:

25. How will the researcher(s) benefit from you being in this study?

TEDDY researchers will talk about the study at scientific meetings. They will write about the study in scientific journals. This may help their careers. This research study might lead to a new treatment or drug. The TEDDY researchers might get credit for the new treatment or drug.

26. Signatures

As a member of the TEDDY study team, I have explained to the participant the purpose, procedures, possible benefits, risks, and the alternatives to being in this research study. I have explained how the participant's Protected Health Information would be collected, used and shared:

_____

Signature of Person Obtaining Consent and Authorization Date

Parent/Adult Legally Representing the Subject. By signing this form, you voluntarily give your permission for the person named below to be in this study. You are not giving up any legal rights for yourself or the person you are legally representing. After your signature, please print your name and your relationship to the subject.

_____

Signature of Parent/Legal Representative Date

_____

Print: Name of Legal Representative of and Relationship to Participant:

Cord Blood Storage

By signing this consent you agree to a one-time screening of your infant's cord blood for genetic markers that indicate risk of future development of type 1 diabetes. The questions below ask for your consent to store a small amount of your child's cord blood and DNA for future testing by the TEDDY Study investigators. You may participate in the one-time screening even if you do not agree to the storage of your child's blood and DNA. Please mark and initial the statements below to indicate whether you agree to the storage of your child's cord blood and DNA for future use. You may withdraw your consent at any time.

I agree that my child's blood/cord blood and DNA may be stored for future testing by the TEDDY Study. I understand that this testing may include medical research projects on diabetes or other medical conditions.

YES_____ NO _____
Initials_____

In the unlikely event that an analysis conducted by the TEDDY Study may become useful to me, I wish the TEDDY Study attempt to inform me of the results of the test and its meaning.

YES_____ NO _____
Initials_____

Future Research Studies

We may want to ask you or your child to be in future research studies. Please tell us below if we may contact you. Your choice does not affect your participation in TEDDY.

YES_____ Initials _____ Please contact me about future studies.

NO_____ Initials _____ Do not contact me about future studies.

_____
Signature of Parent/Legal Representative Date

_____
Print: Name of Legal Representative of and Relationship to Participant:

C. Site Specific Screening Informed Consents

1. Colorado
2. Finland
3. Germany
4. Georgia/Florida
5. Sweden
6. Washington

C1. Site Specific Screening Informed Consents: Colorado for First Degree Relatives

Consent Form Approval ID:

Date: _____ Valid For Use Through: 06.25.2007

COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD

Title: The Environmental Determinants of Diabetes in the Young (TEDDY) Study
COMIRB Protocol 04-0361

Approved
MAY 26 2006
COMIRB

Principal Investigator: Marian Rewers, MD, PhD
SUBJECT CONSENT TO GENETIC SCREENING
(First-Degree Relative Cohort)
October 13, 2005

Project Description

You = (you /your child) are being asked to take part in a research study at the University of Colorado School of Medicine to learn about the possible causes of type 1 diabetes mellitus (T1DM) in children who have a greater chance of getting T1DM. T1DM used to be called childhood diabetes or insulin-dependent diabetes. You are being asked to take part in this research study because you are a first degree relative (sibling or child) of someone who has been diagnosed with T1DM.

Purpose of Consent: The purpose of this consent is to explain the research project and what will be involved if you decide to take part. The Principal Investigator (the person in charge of this research) or a representative of the study will also describe this study to you and answer all of your questions. Before you decide whether or not to take part in this research study, read the information below and ask questions about anything you do not understand. Your participation is entirely voluntary. You will be given a copy of this form for your records. As a parent, you must consent to have your child participate.

Study Rationale: This study is divided into two parts. Part 1 screens newborns for higher risk diabetes genes. Part 2 will follow children identified as having higher risk genes for 15 years to learn about possible environmental factors that may cause T1DM. **This consent form describes the participation in part 1 of the study: the screening for diabetes gene markers.**

T1DM can happen at any age but is more common in childhood and occurs most in people who are born with certain genes. Children who have these genes are at higher risk for getting diabetes. However, not all children who are at higher risk get diabetes. Not having these genes, however, does not guarantee that your child will not get diabetes. It is the purpose of this study to try and find out what environmental factors are important in developing T1DM, and why some children with higher risk genes get T1DM and some do not. When we understand these things, we can then try to prevent the disease. Six groups of research doctors from across the world, 3 groups in the United States (Colorado, Washington and Georgia) and 3 groups in Europe (Sweden, Finland, and Germany) are working together to learn which environmental factors are important in developing T1DM.

T1DM happens when the immune system that normally protects the body from infection becomes confused and attacks and destroys the insulin producing cells (islet cells) in the pancreas. Insulin is necessary for the body to turn food into energy. Insulin helps to keep the sugar in the blood at a normal level. Without insulin, a person's blood sugar becomes too high and this makes the person sick. High blood sugar is treated with a few daily insulin shots. What actually causes the immune system to attack the insulin producing cells in the pancreas is still unknown. We can see the immune system attacking the insulin producing cells by testing the blood for autoantibodies. These autoantibodies can be seen in the blood months or even years before someone has T1DM.

Initials_____

If you agree to be in the study, you understand that:

- You agree to have your child's blood screened for higher risk diabetes genes.
- Up to 1,000 children in the Denver Area will be taking part in this part of the study.
- Your participation is voluntary.

Procedures

To screen your baby for these genetic markers, we would like to test your baby's umbilical cord blood or obtain blood from a heel stick. The blood sample will be used to obtain DNA (the part of the blood that carries your baby's genes).

Umbilical cord blood: When your baby is born, we would like to have no more than 7ml (less than 2 teaspoons) of his or her umbilical cord blood collected by your Obstetrician or Health Care Provider for this testing. We will provide the necessary supplies and instructions to collect this blood sample. Umbilical cord blood is routinely collected. This is blood that remains in the cord and placenta and is not needed by you or your baby after the birth. There is no feeling in the umbilical cord so this will in no way harm you or your baby. You will send this sample to the TEDDY clinic in shipping boxes we provide. We will then send it to the genetic testing lab.

Or:

Heel stick: Before your child is 4 months old, you may bring your infant to the TEDDY clinic for the procedure. About 8-10 drops (less than ½ teaspoon) of blood will be drawn from your baby by heel stick. This is the standard way to get blood from infants for routine laboratory tests. Usually enough blood can be obtained with one heel stick. In the event more blood is needed, your child will have no more than 2 heel sticks.

TEDDY will send the blood sample to a laboratory in California where screening for the diabetes gene markers will be done. Part of the sample will be kept as a backup at the TEDDY Colorado facility. Your child's name will not be on the blood sample; it will only have a number on it. The laboratory will send the results back to the TEDDY researchers and we will tell only you of the results. We will explain what having these genes mean in terms of diabetes risk and answer any questions you may have. At this time, the gene testing we do will not help your child's doctor in any way with any treatment. This testing cannot determine or rule out paternity or maternity of the child.

If your baby does not have the higher-risk genes for T1DM, you will receive a letter from the TEDDY Study stating that and no further participation in second part of this study will be offered. We will tell you other ways to follow and re-test your child if you wish to do so.

If your baby does have the high-risk genes, the TEDDY Study will call and send you a postcard within 12 weeks notifying you that the results are in. When we speak with you we will explain the results and you will have the opportunity to enroll your child in the second part of this study. We will explain the second part of this study fully when the results of the testing are available. You can then decide whether or not to give your consent for your child to participate further. Part 2 of the study will follow babies with higher-risk genes to see why some babies get T1DM and others do not. We will be looking for possible environmental factors leading to the development of T1DM.

Discomforts and Risks

Umbilical cord blood: For testing of umbilical cord blood there is no risk of injury resulting from your participation. You will not be poked to obtain this sample.

Heel stick: If the blood comes from a heel stick, some discomfort may be felt the moment the needle goes into the skin and your baby may cry. In about 1 in 10 cases a small about of bleeding under the skin will produce a bruise. A small scar may be seen for several weeks. The risk of local infection is less than 1 in a 1000.

If you are planning to save or "bank" the cord blood for potential later use, the small amount of blood needed for TEDDY screening (1-2% of the cord blood) will not significantly reduce the amount of available for cord blood banking storage.

Initials_____

If you have a higher-risk gene for T1DM you may feel worried or stressed. Some people may also worry that a person with a higher-risk gene might be denied health insurance or life insurance. It is very important to us to keep your test results confidential. To protect you, we will not tell anyone else about your genes. We will keep your genetic information in locked files. You will be given a number so names will not be used. Only members of the TEDDY study team will be able to use the locked files. No information will be put in your medical record by the study staff.

It is **your** decision whether or not to tell your baby's doctor of these test results or to place the results in the medical record. If you choose to have these results placed in your medical record, there is a small possibility that health, disability, and life insurance companies may interpret these screening results incorrectly and this may affect your ability to get medical or life insurance in the future. The only way insurance companies would know of these test results is if **you** told them directly or if the results were in the medical record.

The study may include risks that are unknown at this time.

Benefits
This study is designed for the researcher to learn more about genetic and environmental factors that affect the risk of developing T1DM. This study is not designed to treat any illness or to improve your health. Also there are risks as mentioned in the Risk Section.

Study Sponsor
The sponsor for this study is the National Institutes of Health (NIH), USA.

Cost to Subject
The genetic screening will be done and reported at no cost to you. You will not be paid for your participation in this study.

Voluntary Participation and Study Withdrawal
Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you do not take part in the study, your doctor will still take care of you. You will not lose any benefits or medical care to which you are entitled.

If you choose to take part, you have the right to stop at any time. If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them.

The study doctor may decide to stop your participation without your permission, if he or she thinks that being in the study may cause you harm, or for any other reason. Also the sponsor may stop the study at any time.

If you decide to drop out of the study by withdrawing your consent for genetic screening, you should contact the Screening Coordinator, Ann Deas at 303-315-7979.

Invitations for Questions
The researcher carrying out this study is Dr. Marian Rewers. We want to answer all of your questions. At any time you are permitted and encouraged to ask any questions about this study. You may ask any questions you have now. If you have questions later, you may call the Study Nurse, Michelle Hoffman, RN, at 303-315-7852, the Project Manager, Judy Baxter, at 303-315-6857, or the Principal Investigator, Marian Rewers, MD, PhD, at 303-724-6757 if there is anything you want to discuss.

If you have questions regarding your rights as a research subject, please call the Colorado Multiple Institutional Review Board (COMIRB) office at 303-724-1055.

Initials_____

Confidentiality
We will make every effort to keep your research records confidential, but it cannot be assured. Records that identify your child or you (including medical records) and the consent form signed by you, may be looked at by the following people:

- Federal agencies that oversee human subject research
- Colorado Multiple Institutional Review Board
- The investigator and research team for the TEDDY Study
- The sponsor or an agent for the sponsor (Dept. of Health and Human Services (DHHS) and the National Institutes of Health (NIH))
- Regulatory officials from the institution where the research is being conducted, to ensure compliance with policies or monitor the safety of the study

DHHS personnel may request identifying information for purposes of performing audits, carrying out investigations of DHHS grant recipients, or evaluating DHHS funded research projects.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Even with the Certificate of Confidentiality, the investigators continue to have ethical and legal obligations to report child abuse or neglect and to prevent you from carrying out any threats to do serious harm to yourself or others. If keeping information private would immediately put you or someone else in danger, the investigators would release information to protect you or another person.

The results of this research may be presented at meetings or in published articles. However, your child's name and/or your name will be kept private. You will also be asked to sign a separate HIPAA authorization form that explains who will have access to your Protected Health Information.

All records will be kept under lock and key. All computerized data files are password protected and your child will be identified only by a code number. All biologic samples will be labeled with a code number only. Any analysis that is done using your child's samples will be identified only by the code. The code cannot be traced back to your name or other identifying information except by authorized study staff and investigators.

Injury and Compensation
You may wish to tell your health care provider if you decide to participate in this research study. However, there may be risks associated with telling your provider your test results as discussed in the Discomforts and Risk section above.

If you have questions about injury related to the research, you may call Dr. Marian Rewers at (303) 724-6757 and/or your private physician. Dr. Rewers should be informed about any injury you experience while you take part in this study.

If you are hurt by this research, we will give you medical care if you want it, but you will have to pay for the care that is needed. If your child is injured by the heel stick procedure, only professional medical care that you receive at the TEDDY clinic will be provided without charge.

Initials_____

AUTHORIZATION

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I know that being in this study is voluntary. I choose to have my child in this study: I know I can stop being in the study and my child will still get the usual medical care. I will get a copy of this consent form. (Please initial all the previous pages of the consent form) _____

Child's Name: _____ Birth date ____/____/____
print name

Parent or Guardian: _____/_____Date:_____
Signature print name

Parent or Guardian: _____/_____Date:_____
Signature print name

I hereby certify that the foregoing document was explained to the subject, and was read and voluntarily signed by the subject or their legal representative who appeared to be of sound mind and not under duress.

Consent forms explained by: _____/_____ Date: _____
Signature print name

Investigator or Designee: _____/_____ Date: _____
Signature print name

ID:

Initials_____

PERMISSION TO STORE REMAINING CORD BLOOD SAMPLE FOR FUTURE RESEARCH

You have just agreed to a one-time screening of your infant's cord blood for genetic markers that indicate risk of future development of type 1 diabetes. This sample will be held until you are notified of the screening results. The questions below ask for your consent to continue store this small amount of your child's leftover cord blood and DNA for future testing by the TEDDY Study investigators. You may participate in the one-time genetic screening even if you do not agree to the storage of your child's blood and DNA for future testing.

Please mark and initial the statements below to indicate whether you agree to continued storage of your child's leftover cord blood and DNA for future use. You may withdraw your consent at any time. To do this you should contact the Screening Coordinator at 303-315-7979.

I agree that my child's blood/cord blood and DNA may be stored for future testing by the TEDDY Study. I understand that this testing may include medical research projects on diabetes or other medical conditions.

☐ **YES** ***Initials____*** ☐ **NO** ***Initials____***

In the unlikely event that an analysis conducted by the TEDDY Study may become useful to me, I wish the TEDDY Study attempt to inform me of the results of the test and its meaning.

☐ **YES** ***Initials____*** ☐ **NO** ***Initials____***

Parent or
Legal Guardian: _____/_____ Date: _____
Signature Print name

Initials_____

C1. Site Specific Screening Informed Consents: Colorado for General Population

Consent Form Approval

ID:

Date: _____ Valid For Use Through: 06.25.2007

COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD

Title: The Environmental Determinants of Diabetes in the Young (TEDDY) Study
COMIRB Protocol 04-0361

Approved
MAY 26 2006 bz
COMIRB bz

Principal Investigator: Marian Rewers, MD, PhD
SUBJECT CONSENT TO GENETIC SCREENING
General Population/Cord Blood Kit Screening
October 13, 2005

Project Description

You = (you /your child) are being asked to take part in a research study at the University of Colorado School of Medicine to learn about the possible causes of type 1 diabetes mellitus (T1DM) in children who have a greater chance of getting T1DM. T1DM used to be called childhood diabetes or insulin-dependent diabetes. You are being asked to take part in this research study because you contacted us about taking part in the study.

Purpose of Consent: The purpose of this consent is to explain the research project and what will be involved if you decide to take part. The Principal Investigator (the person in charge of this research) or a representative of the study will also describe this study to you and answer all of your questions. Before you decide whether or not to take part in this research study, read the information below and ask questions about anything you do not understand. Your participation is entirely voluntary. You will be given a copy of this form for your records. As a parent, you must consent to have your child participate.

Study Rationale: This study is divided into two parts. Part 1 screens newborns for higher risk diabetes genes. Part 2 will follow children identified as having higher risk genes for 15 years to learn about possible environmental factors that may cause T1DM. **This consent form describes the participation in part 1 of the study: the screening for diabetes gene markers.**

T1DM can happen at any age but is more common in childhood and occurs most in people who are born with certain genes. Children who have these genes are at higher risk for getting diabetes. However, not all children who are at higher risk get diabetes. Not having these genes, however, does not guarantee that your child will not get diabetes. It is the purpose of this study to try and find out what environmental factors are important in developing T1DM, and why some children with higher risk genes get T1DM and some do not. When we understand these things, we can then try to prevent the disease. Six groups of research doctors from across the world, 3 groups in the United States (Colorado, Washington and Georgia) and 3 groups in Europe (Sweden, Finland, and Germany) are working together to learn which environmental factors are important in developing T1DM.

T1DM happens when the immune system that normally protects the body from infection becomes confused and attacks and destroys the insulin producing cells (islet cells) in the pancreas. Insulin is necessary for the body to turn food into energy. Insulin helps to keep the sugar in the blood at a normal level. Without insulin, a person's blood sugar becomes too high and this makes the person sick. High blood sugar is treated with a few daily insulin shots. What actually causes the immune system to attack the insulin producing cells in the pancreas is still unknown. We can see the immune system attacking the insulin producing cells by testing the blood for autoantibodies. These autoantibodies can be seen in the blood months or even years before someone has T1DM.

Initials_____

If you agree to be in the study, you understand that:

- You agree to have your child's blood screened for higher risk diabetes genes.
- Up to 60,000 babies in the Denver Area, & up to 220,000 babies across the world will be taking part in this study.
- Your participation is voluntary.

Procedures

To screen your baby for these genetic markers, we would like to test your baby's umbilical cord blood **or** obtain blood from a heel stick. The blood sample will be used to obtain DNA (the part of the blood that carries your baby's genes).

Umbilical cord blood: When your baby is born, we would like to have no more than 7ml (less than 2 teaspoons) of his or her umbilical cord blood collected by your Obstetrician or Health Care Provider for this testing. We will provide the necessary supplies and instructions to collect this blood sample. Umbilical cord blood is routinely collected. This is blood that remains in the cord and placenta and is not needed by you or your baby after the birth. There is no feeling in the umbilical cord so this will in no way harm you or your baby. You will send this sample to the TEDDY clinic in shipping boxes we provide. We will then send it to the genetic testing lab.

Or:

Heel stick: Before your child is 4 months old, you may bring your infant to the TEDDY clinic for the procedure. About 8-10 drops (less than ½ teaspoon) of blood will be drawn from your baby by heel stick. This is the standard way to get blood from infants for routine laboratory tests. Usually enough blood can be obtained with one heel stick. In the event more blood is needed, your child will have no more than 2 heel sticks.

TEDDY will send the blood sample to a laboratory in California where screening for the diabetes gene markers will be done. Part of the sample will be kept as a backup at the TEDDY Colorado facility. Your child's name will not be on the blood sample; it will only have a number on it. The laboratory will send the results back to the TEDDY researchers and we will tell only you of the results. We will explain what having these genes mean in terms of diabetes risk and answer any questions you may have. At this time, the gene testing we do will not help your child's doctor in any way with any treatment. This testing cannot determine or rule out paternity or maternity of the child.

If your baby does not have the higher-risk genes for T1DM, you will receive a letter from the TEDDY Study stating that and no further participation in second part of this study will be offered. We will tell you other ways to follow and re-test your child if you wish to do so.

If your baby does have the high-risk genes, the TEDDY Study will call and send you a postcard within 12 weeks notifying you that the results are in. When we speak with you we will explain the results and you will have the opportunity to enroll your child in the second part of this study. We will explain the second part of this study fully when the results of the testing are available. You can then decide whether or not to give your consent for your child to participate further. Part 2 of the study will follow babies with higher risk genes to see why some babies get T1DM and others do not. We will be looking for possible environmental factors leading to the development of T1DM.

Discomforts and Risks

Umbilical cord blood: For testing of umbilical cord blood there is no risk of injury resulting from your participation. You will not be poked to obtain this sample.

Heel stick: If the blood comes from a heel stick, some discomfort may be felt the moment the needle goes into the skin and your baby may cry. In about 1 in 10 cases a small about of bleeding under the skin will produce a bruise. A small scar may be seen for several weeks. The risk of local infection is less than 1 in a 1000.

If you are planning to save or "bank" the cord blood for potential later use, the small amount of blood needed for TEDDY screening (1-2% of the cord blood) will not significantly reduce the amount of available for cord blood banking storage.

Initials_____

If you have a higher-risk gene for T1DM you may feel worried or stressed. Some people may also worry that a person with a higher-risk gene might be denied health insurance or life insurance. It is very important to us to keep your test results confidential. To protect you, we will not tell anyone else about your genes. We will keep your genetic information in locked files. You will be given a number so names will not be used. Only members of the TEDDY study team will be able to use the locked files. No information will be put in your medical record by the study staff.

It is **your** decision whether or not to tell your baby's doctor of these test results or to place the results in the medical record. If you choose to have these results placed in your medical record, there is a small possibility that health, disability, and life insurance companies may interpret these screening results incorrectly and this may affect your ability to get medical or life insurance in the future. The only way insurance companies would know of these test results is if **you** told them directly or if the results were in the medical record.

The study may include risks that are unknown at this time.

Benefits
This study is designed for the researcher to learn more about genetic and environmental factors that affect the risk of developing T1DM. This study is not designed to treat any illness or to improve your health. Also there are risks as mentioned in the Risk Section.

Study Sponsor
The sponsor for this study is the National Institutes of Health (NIH), USA.

Cost to Subject
The genetic screening will be done and reported at no cost to you. You will not be paid for your participation in this study.

Voluntary Participation and Study Withdrawal
Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you do not take part in the study, your doctor will still take care of you. You will not lose any benefits or medical care to which you are entitled.

If you choose to take part, you have the right to stop at any time. If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them.

The study doctor may decide to stop your participation without your permission, if he or she thinks that being in the study may cause you harm, or for any other reason. Also the sponsor may stop the study at any time.

If you decide to drop out of the study by withdrawing your consent for genetic screening, you should contact the Screening Coordinator, Ann Deas at 303-315-7979.

Invitations for Questions
The researcher carrying out this study is Dr. Marian Rewers. We want to answer all of your questions. At any time you are permitted and encouraged to ask any questions about this study. You may ask any questions you have now. If you have questions later, you may call the Study Nurse, Michelle Hoffman, RN, at 303-315-7852, the Project Manager, Judy Baxter, at 303-315-6857, or the Principal Investigator, Marian Rewers, MD, PhD, at 303-724-6757 if there is anything you want to discuss.

If you have questions regarding your rights as a research subject, please call the Colorado Multiple Institutional Review Board (COMIRB) office at 303-724-1055.

Initials_____

Confidentiality
We will make every effort to keep your research records confidential, but it cannot be assured. Records that identify your child or you (including medical records) and the consent form signed by you, may be looked at by the following people:

- Federal agencies that oversee human subject research
- Colorado Multiple Institutional Review Board
- The investigator and research team for the TEDDY Study
- The sponsor or an agent for the sponsor (Dept. of Health and Human Services (DHHS) and the National Institutes of Health (NIH))
- Regulatory officials from the institution where the research is being conducted, to ensure compliance with policies or monitor the safety of the study

DHHS personnel may request identifying information for purposes of performing audits, carrying out investigations of DHHS grant recipients, or evaluating DHHS funded research projects.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Even with the Certificate of Confidentiality, the investigators continue to have ethical and legal obligations to report child abuse or neglect and to prevent you from carrying out any threats to do serious harm to yourself or others. If keeping information private would immediately put you or someone else in danger, the investigators would release information to protect you or another person.

The results of this research may be presented at meetings or in published articles. However, your child's name and/or your name will be kept private. You will also be asked to sign a separate HIPAA authorization form that explains who will have access to your Protected Health Information.

All records will be kept under lock and key. All computerized data files are password protected and your child will be identified only by a code number. All biologic samples will be labeled with a code number only. Any analysis that is done using your child's samples will be identified only by the code. The code cannot be traced back to your name or other identifying information except by authorized study staff and investigators.

Injury and Compensation
You may wish to tell your health care provider if you decide to participate in this research study. However, there may be risks associated with telling your provider your test results as discussed in the Discomforts and Risk section above.

If you have questions about injury related to the research, you may call Dr. Marian Rewers at (303) 724-6757 and/or your private physician. Dr. Rewers should be informed about any injury you experience while you take part in this study.

If you are hurt by this research, we will give you medical care if you want it, but you will have to pay for the care that is needed. If your child is injured by the heel stick procedure, only professional medical care that you receive at the TEDDY clinic will be provided without charge.

Initials_____

AUTHORIZATION

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I know that being in this study is voluntary. I choose to have my child in this study: I know I can stop being in the study and my child will still get the usual medical care. I will get a copy of this consent form. (Please initial all the previous pages of the consent form)

Child's Name: _____ Birth date ____/____/____
print name

Parent or Guardian: _____/_____Date:_____
Signature print name

Parent or Guardian: _____/_____Date:_____
Signature print name

I hereby certify that the foregoing document was explained to the subject, and was read and voluntarily signed by the subject or their legal representative who appeared to be of sound mind and not under duress.

Consent forms explained by: _____/_____ Date: _____
Signature print name

Investigator or Designee: _____/_____ Date: _____
Signature print name

ID:

Initials_____

PERMISSION TO STORE REMAINING CORD BLOOD SAMPLE FOR FUTURE RESEARCH

You have just agreed to a one-time screening of your infant's cord blood for genetic markers that indicate risk of future development of type 1 diabetes. This sample will be held until you are notified of the screening results. The questions below ask for your consent to continue store this small amount of your child's leftover cord blood and DNA for future testing by the TEDDY Study investigators. You may participate in the one-time genetic screening even if you do not agree to the storage of your child's blood and DNA for future testing.

Please mark and initial the statements below to indicate whether you agree to continued storage of your child's leftover cord blood and DNA for future use. You may withdraw your consent at any time. To do this you should contact the Screening Coordinator at 303-315-7979.

I agree that my child's blood/cord blood and DNA may be stored for future testing by the TEDDY Study. I understand that this testing may include medical research projects on diabetes or other medical conditions.

☐ **YES** ***Initials____*** ☐ **NO** ***Initials____***

In the unlikely event that an analysis conducted by the TEDDY Study may become useful to me, I wish the TEDDY Study attempt to inform me of the results of the test and its meaning.

☐ **YES** ***Initials____*** ☐ **NO** ***Initials____***

Parent or
Legal Guardian: _____/_____ Date: _____
Signature Print name

Initials_____

C2. Site Specific Screening Informed Consents: Finland

THIS COPY IS FOR THE RESEARCH GROUP/FAMILY

INFORMED CONSENT IN THE STUDY
"PREDICTION AND PREVENTION OF TYPE 1 DIABETES"
(PART 1: Determination of diabetes risk genes in a blood sample from umbilical cord blood)

I/we have read and understood the information in the brochure on diabetes prediction and prevention study. I/we give our permission to investigate if our child has increased genetic risk for diabetes from a blood sample that was taken from his/her umbilical cord after delivery. We will receive the results and information of possible further measures by phone or in a letter about two months after the child was born.

I/we give permission to investigate diabetes risk gene from the umbilical cord blood sample of our child.

Check the option you choose: **yes** ☐ **no** ☐

_____

Date Mother´s / father´s signature and name in block letters

Street address_____

Post office code _____

Telephone _____

_____

Date The name and singnature of the person who received the consent

PLEASE TURN !PAGE

PLEASE RETURN TO THE NURSES

Dear parents!

Congratulations for the new member in your family!
Please fill this form, where we ask some information on your family memebers.

MOTHER OF THE BABY:
Date of birth and ID ____ ____ ____-____
First names .....
Last name (also previous) :.....

NEWBORN
Date of birth ____ ____ ____
(if you gave birth to twins or triplets, please fill in the information about all of them)

Baby (A)	Baby (B)	Baby (C)
☐ Boy	☐ Boy	☐ Boy
☐ Girl	☐ Girl	☐ Girl

Name: .....

THIS COPY IS FOR THE RESEARCH GROUP/FAMILY

OTHER CHILDREN IN OUR FAMILY:
The number of children in our family is : _____

Year of birth _____
Sex ☐ Boy ☐ Girl

Year of birth _____
Sex ☐ Boy ☐ Girl

Year of birth _____
Sex ☐ Boy ☐ Girl

Year of birth _____
Sex ☐ Boy ☐ Girl

HAS ANY OF THE FOLLOWING PERSONS TYPE 1 DIABETES?

- The mother of the baby ☐ Yes ☐ No
- The father of the baby ☐ Yes ☐ No
- One of the full sisters or brothers of the baby ☐ Yes ☐ No

PLEASE TURN !PAGE

PLEASE RETURN TO THE NURSES

Thank you on behalf of the Research Group!

Professor Olli Simell
Department of Pediatrics,
University of Turku

TEDDY/DIPP 210904

C3. Site Specific Screening Informed Consents: Germany

Einverständniserklärung zur Teilnahme an der TEDDY-Studie

(Teil 1: Untersuchung des genetischen Risikos)

Nur die TEDDY-Mitarbeiter vom Institut für Diabetesforschung in München, haben im Rahmen der entsprechenden gesetzlichen Vorschriften Zugang zu den vertraulichen Daten, in denen Ihr Kind namentlich genannt wird. Diese Personen unterliegen der Schweigepflicht und sind zur Beachtung des Datenschutzes verpflichtet. Die Weitergabe der Daten im In- und Ausland erfolgt ausschließlich zu statistischen und wissenschaftlichen Zwecken, und Ihr Kind wird ausnahmslos darin nicht namentlich genannt. Auch in etwaigen Veröffentlichungen der Daten dieser Studie wird Ihr Kind nicht namentlich genannt.

1. **Name des teilnehmenden Kindes:**

   _____

2. **Unterschrift**

   Als ein Mitglied des **TEDDY-Studienteams**, habe ich dem Teilnehmer den Zweck, das Verfahren, den möglich Nutzen und die Gefahren der Teilnahme an dieser Studie erklärt. Ich habe erklärt, wie Daten der Teilnehmer gesammelt, verwendet und gespeichert werden.

   _____

   Unterschrift des TEDDY-Mitarbeiters Datum

   Elternteil / Erziehungsberechtigter. Durch die Unterzeichnung dieses Formulars geben Sie freiwillig Ihre Erlaubnis zur Teilnahme des oben genannten Kindes an der TEDDY-Studie und zur Verwertung der pseudonymisierten Daten.

   _____

   Unterschrift des Elternteils/Erziehungsberechtigten Datum

   _____

   In Druckschrift: Name des Elternteils/Erziehungsberechtigten und Verhältnis zum teilnehmenden Kind.

   _____

   Unterschrift des 2. einwilligenden Elternteils Datum

INSTITUT FÜR DIABETESFORSCHUNG

Prof. Dr. med. Anette-G. Ziegler
Leiterin der Klin. exp. Abteilung am Institut für Diabetesforschung und
Ltd. Oberärztin der 3.Med. Abt. am Städt. Krankenhaus München-Schwabing
KÖLNER PLATZ 1, D-80804 MÜNCHEN, TELEFON 089-30793121, TELEFAX 089-3081733

Informationen zur TEDDY-Studie und Einverständniserklärung Teil 1

Wir möchten Ihnen gerne die TEDDY-Studie vorstellen; eine Studie, die den Einfluss von Umweltfaktoren auf die Entstehung des Typ 1 Diabetes („Jugendlicher Diabetes") untersucht, und Sie zu einer Teilnahme an dieser Studie einladen.

Dieses Schreiben ist dazu gedacht, Ihnen die wichtigsten Informationen zur Studie zu geben. Gerne besprechen wir in einem persönlichen Gespräch die Studie ausführlich und beantworten alle Ihre Fragen.

1. **Wer leitet die Studie?**

   TEDDY ist eine internationale Studie, die in Deutschland unter der Leitung von Frau Prof. Dr. Anette-G. Ziegler am Institut für Diabetesforschung in München durchgeführt wird. Neben dem Münchner Zentrum sind weitere 5 Forschungszentren in Schweden, Finnland und den USA an der Studie beteiligt. Finanziert wird die Studie vom National Institutes of Health (Nationales Gesundheitsinstitut), USA.

2. **Was ist der Zweck dieser Studie?**

   Mit einer Teilnahme an der Studie können Sie uns dabei unterstützen, die Ursachen der Entstehung des Typ 1 Diabetes mellitus herauszufinden. Typ 1 Diabetes wird gewöhnlich auch als „jugendlicher" oder „Insulin-abhängiger Diabetes" bezeichnet. Die Erkrankung Typ 1 Diabetes tritt auf, wenn spezielle Zellen im Körper, die so genannten Betazellen der Bauchspeicheldrüse, durch körpereigene Abwehrzellen zerstört werden. Die Betazellen sind dafür verantwortlich, Insulin zu produzieren. Insulin ist erforderlich, damit der Körper aufgenommene Nahrung verwerten, und die Höhe des Blutzuckerspiegels normal gehalten werden kann. Wenn ein Großteil der Betazellen in der Bauchspeicheldrüse zerstört ist, kann der Körper nicht mehr ausreichend Insulin bilden. Dies führt zu einem Anstieg des Blutzuckers, somit zu einem Diabetes mit möglichen Folgeerkrankungen. Entwickelt ein Kind Typ 1 Diabetes, muss es also täglich mehrmals Insulin spritzen.

   Studien zeigen, dass Kinder mit bestimmten Vererbungsmerkmalen (Genen) ein erhöhtes Risiko aufweisen, später an Typ 1 Diabetes zu erkranken, deshalb möchten wir den HLA-Genotyp Ihres Kindes bestimmen. Merkmale für die Blutgruppenbestimmung liegen auf den roten Blutkörperchen, hingegen werden für die HLA-Bestimmung die weißen Blutkörperchen benötigt, auf deren Oberfläche die verschiedenen HLA- Vererbungsmerkmale präsentiert werden. Jedoch bekommen nicht alle Kinder, die diese Hoch-Risikogene aufweisen,

Diabetes. Wir denken, dass andere Faktoren wie zum Beispiel Umweltfaktoren hinzukommen müssen, die bei Kindern mit den Hoch-Risikogenen dann tatsächlich den Diabetes auslösen. Ziel dieser Studie ist, herauszufinden, welche Faktoren oder Auslöser bewirken, dass Kinder Diabetes bekommen.

Im ersten Schritt will die TEDDY-Studie bei Kindern untersuchen, ob sie Diabetes-Risikogene aufweisen. Die meisten Kinder haben kein Hoch-Risikogen für Typ 1 Diabetes. Im zweiten Schritt der TEDDY-Studie hoffen wir herauszufinden, welche möglichen Umweltfaktoren bei Kindern mit Hoch-Risikogenen die Erkrankung Typ 1 Diabetes verursachen bzw. auslösen können.

Um diese Studie erfolgreich durchführen zu können, müssen genügend Kinder mit Hoch-Risikogenen untersucht werden. Um genügend Kinder mit Hoch-Risikogenen zu finden, werden wir dafür mehr als 220 000 Kinder auf der ganzen Welt untersuchen müssen. Deshalb möchten wir auch Sie um Ihre Teilnahme an der TEDDY-Studie bitten.

3. Was wird unternommen, wenn Sie an dieser Studie teilnehmen?

Die Bestimmung der Diabetes-Risikogene erfolgt aus einer Blutprobe Ihres Kindes. Für diese Untersuchung ist die Blutabnahme kurz nach der Geburt Ihres Kindes aus der Nabelschnur von Vorteil. Die Blutentnahme erfolgt dabei nach Durchtrennung der Nabelschnur. Es besteht jedoch auch die Möglichkeit, zu einem späteren Zeitpunkt (bis zu einem Alter von 3 Monaten) Blut aus der Vene zu entnehmen.

Was wird mit dem Blut Ihres Kindes gemacht? Das Blut Ihres Kindes wird an ein Labor geschickt, das prüft, ob bei Ihrem Kind Hoch-Risikogene für Typ 1 Diabetes vorliegen.

Falls Ihr Kind kein Hoch-Risikogen für Typ 1 Diabetes hat, werden Sie von uns einen Brief mit dieser Nachricht erhalten. Falls Ihr Kind ein Hoch-Risikogen aufweist, werden wir Sie innerhalb von 12 Wochen anrufen. Ihr Kind könnte dann, Ihr erneutes Einverständnis vorausgesetzt, für den zweiten Teil unserer Studie angemeldet werden. Wir werden Kinder mit Hoch-Risikogenen beobachten, um herauszufinden, warum einige Kinder Typ 1 Diabetes bekommen und andere nicht. Wir werden nach möglichen Umweltfaktoren suchen, die zur Entwicklung von Typ 1 Diabetes führen.

Möglicherweise reagieren Sie mit verstärkter Angst und Depression wenn Sie über ein erhöhtes Diabetesrisiko Ihres Kindes unterrichtet werden. Wir werden deshalb mit einem speziellen Fragebogen nach Ihrer Reaktion auf die Ergebnismitteilung fragen und bei deutlich erhöhten Angst- und Depressionswerten eine spezielle Beratung und Betreuung durch eine/n Psycholgen/in vermitteln.

4. Was sind die möglichen Risiken einer Teilnahme?

Die Blutabnahme kurz nach der Geburt aus der Nabelschnur stellt für das Kind keinerlei Gefahr oder Risiko dar. Falls das Blut nach der Geburt aus der Vene entnommen wird, wird das Baby möglicherweise weinen. Es könnte zu einem Bluterguss, einer Schwellung oder einer Infektion kommen. Das Risiko für eine Infektion ist sehr gering.

5. a. Was ist Ihr möglicher Nutzen einer Teilnahme an der TEDDY-Studie?

Wenn Ihr Baby ein Hoch-Risikogen für Typ 1 Diabetes, kann Ihr Baby im zweiten Teil der Studie weiteruntersucht werden. Wir werden Ihnen dann alle neuen Informationen mitteilen, die wir über die Ursachen des Typ 1 Diabetes

herausfinden und Sie über eine mögliche Teilnahme an Studien zum Verhindern von Diabetes aufklären. Wenn Ihr Kind tatsächlich an Typ 1 Diabetes erkranken sollte, könnten wir den Ausbruch der Erkrankung bei einer Teilnahme an der Studie früher feststellen, d.h. bevor Ihr Kind die typischen Symptome für den Typ 1 Diabetes aufweist. Wir würden Sie über alle möglichen Studien informieren, in denen Kinder mit neu diagnostiziertem Typ 1 Diabetes behandelt werden.

b. Was ist der mögliche Nutzen für andere?

Die Ergebnisse dieser Studie werden uns helfen zu verstehen, warum einige Kinder mit Hoch-Risikogenen Typ 1 Diabetes bekommen, während andere Kinder mit den gleichen Genen nicht erkranken. Wenn wir das verstehen, können wir versuchen, diese Krankheit zu verhindern bzw. zu heilen.

6. **Ist eine Teilnahme an der TEDDY-Studie für Sie mit Kosten verbunden?**

   Nein.

7. **Werden Sie einen Ausgleich für die Teilnahme an dieser Studie erhalten?**

   Sie werden nicht für die Teilnahme an dieser Studie bezahlt.

8. **a. Können Sie die Teilnahme an dieser Studie widerrufen?**

   Die Teilnahme an der TEDDY-Studie ist freiwillig. Sie können jederzeit die Teilnahme an der Studie ohne Nennung von Gründen beenden. Wenn Sie sich entscheiden, die Teilnahme zu beenden, sollten Sie mit Frau Christiane Winkler am Institut für Diabetesforschung (Tel. 089/30793114) in Verbindung treten.

   b. Kann der Studienleiter Sie von der Studienteilnahme ausschließen?

   Sie können aus der Studie ausgeschlossen werden, wenn Sie nicht die Anforderungen erfüllen. Das National Institutes of Health, das diese Studie finanziert, kann jederzeit die Weiterführung der Studie beenden.

9. **Wie wird die Vertraulichkeit Ihrer Daten gewährleistet?**

   Die Ergebnisse der genetischen Untersuchung Ihres Kindes sowie alle weiteren Daten, die im Rahmen dieser Untersuchung gesammelt werden, können nur von TEDDY-Mitarbeitern vom Institut für Diabetesforschung eingesehen werden. Wir werden die Daten niemandem, auch nicht Ihrem behandelnden Arzt, ohne Ihre Erlaubnis zeigen.

   Die Daten werden auf EDV gespeichert, ausschließlich zu wissenschaftlichen und statistischen Zwecken verwendet und dazu nie in Verbindung mit Ihrem Namen oder dem Namen Ihres Kindes verwendet. Ihre Daten werden pseudonymisiert, das bedeutet jedem Studienkind und jeder biologischen Probe wird im Institut für Diabetesforschung eine Codenummer zugewiesen. Ein Personenbezug kann nur durch Dritte wiederhergestellt werden.

   Wie lange werden Ihre Daten gesammelt und gespeichert?

   Die Daten bzw. die Daten Ihres Kindes werden nach Abschluss der Studie gelöscht.

10. **Können Sie Ihre Daten bzw. die Daten Ihres Kindes einsehen oder kopieren?**

    Sie erhalten eine Mitteilung über die Einschätzung des Diabetes-Risikos Ihres Kindes.

11. Können Sie Ihr Einverständnis zur Sammlung und Verwendung Ihrer Daten bzw. der Daten Ihres Kindes widerrufen?

Ja, Sie können jederzeit die Teilnahme an der Studie beenden, dann werden keine neuen Informationen über Sie oder Ihr Kind gesammelt, es sei denn, Sie erlauben uns, jährlich mit Ihnen in Verbindung zu treten um Ihnen einige Frage über die Gesundheit Ihres Kindes zu stellen. Informationen, die wir jedoch bis zu dem Zeitpunkt von Ihnen erhalten haben, können für statistische und wissenschaftliche Zwecke weiterverwendet werden. Wenn Sie nicht wünschen, dass wir diese Informationen verwenden, teilen Sie uns dies bitte in einem Schreiben mit.

12. Welchen Nutzen wird das TEDDY-Studienteam aus Ihrer Studienteilnahme ziehen?

Die TEDDY Mitarbeiter werden bei wissenschaftlichen Sitzungen und in wissenschaftlichen Zeitschriften über die Studie und deren Ergebnisse berichten. Des weiteren kann die TEDDY-Studie zur Entwicklung einer neuen Form der Verhinderung oder Behandlung des Typ 1 Diabetes führen.

Sollten Sie weitere Fragen zur Teilnahme an der TEDDY-Studie haben, beantworten wir diese gerne in einem persönlichen Gespräch.

KONTAKT-ADRESSE:

Frau Christiane Winkler / Frau Prof. Dr. med. Anette-G. Ziegler
Institut für Diabetesforschung
Kölner Platz 1
80804 München
Tel. 089-3079 3114
Fax. 089-3081733
e-mail: Teddy.Germany@lrz.uni-muenchen.de

C4. Site Specific Screening Informed Consents: Georgia/Florida

Subject's name_____

Medical College of Georgia
GEORGIA'S HEALTH SCIENCES UNIVERSITY

Parental/Guardian Research Informed Consent Document

Protocol Title:
The Environmental Determinants of Diabetes in the Young (TEDDY) - Part 1: Screening
Principal Investigator's Name: Jin-Xiong She, Ph.D.
Sub-Investigators' Names: Andrew Muir, MD, Diane Hopkins, MS, Leigh Steed, RN, YiHua Huang, Ph.D., Richard A. McIndoe, Ph.D., Nellie Jenkins, Deana McFeely, Michelle Pounders
Sponsor's Name: National Institutes of Health

My child is 1 of 100,000 newborns in Georgia who is being invited to enroll in TEDDY, a research study of the causes of type 1 diabetes mellitus (T1DM). After I review this consent form, TEDDY staff will answer my questions. If I have questions after I sign this consent form, I may call the Principal Investigator, Dr. She or the TEDDY Coordinator, Mrs. Hopkins at 721-4161 or 1-888-225-7785.

Purpose and Design of the Research Study
Part 1 of TEDDY uses gene tests to identify newborns who may be at high risk of someday getting T1DM. I will be asked to provide my contact information and my family history of diabetes. About 3-5 drops of blood will be obtained either from my baby's umbilical cord or heel. Whenever possible, heel samples will be obtained when blood is already being taken for tests that the State requires from all newborns. The blood samples will be used to perform tests to determine the risk for T1DM and the remaining samples will be stored in Dr. She's laboratory. The samples may be sent to another laboratory for confirmation of the test results. The results of my baby's T1DM gene tests will be reported to me within 12 weeks. With my baby's identification removed from the report, the test results will be sent electronically to the TEDDY data coordinating center.

What are the possible discomforts and risks?
Cord blood sampling causes no pain. A heel stick may cause discomfort at the site of the needle stick, possible bruising and swelling around the injection site, and rarely, an infection.
Genetic information may cause harm, for example, by causing anxiety in my family, discrimination in my child's insurability, or unpredicted disclosure of genetic information. The DNA sample and results from my baby will therefore be coded; the codes will be kept in locked files and will be known only to the investigators. Computer databases containing study information will be protected by passwords. Psychological support to my family will be made available as needed.

What are the possible benefits to my child or others?
If my baby has high-risk genes for T1DM, he or she will be eligible for Part 2 of the study. Part 2 participants will be told of important information learned from TEDDY and will be told if they are eligible for studies to prevent T1DM. Early diagnosis of T1DM occurs frequently in children in studies like TEDDY and this prevents them from getting very sick before receiving treatment.
The results of this study will help us understand why some children with high-risk genes get T1DM while other children with the same genes do not. Researchers help their careers by publishing results of TEDDY in scientific meetings and journals.

HAC FILE # 04-05-380
HAC APPROVED INFORMED CONSENT DOCUMENT
APPROVAL FROM 05/24/07 TO 05/23/08
THIS DOCUMENT IS NO LONGER VALID TO ENROLL SUBJECTS AFTER THIS DATE.

Initials_____

Subject's name_____

Costs
I will not be charged any fee for the TEDDY lab tests, nor will I be paid for participating.

What if my child is injured because of the study?
The chance of my child being injured by a study procedure is very low. The Medical College of Georgia (MCG) or MCG Health, Inc. assumes no obligation to pay any money or provide free medical care in case this project results in any harm to my child. The exact costs cannot be determined at this time since any harm to my child would be unforeseen. My insurance company may not pay for such treatments, in which case payment of the costs will be my responsibility. By agreeing to this, I do not give up my rights to seek compensation in the courts. In case of a study-related medical emergency, Dr. Andrew Muir, may be reached 24 hours a day, seven days a week at 706-721-4158. If I have any questions or concerns about the rights of research subjects, I may contact the Chairman of the Human Assurance Committee, George S. Schuster, D.D.S., Ph.D. at 706-721-2991.

What other options or treatments are available if I do not want to be in this study?
I may choose not to participate in TEDDY without this decision affecting my child's or my care.

Can I withdraw from this research study?
My child's participation in this study is voluntary. I can drop out of this study at any time. There are no penalties for dropping out, nor will I lose any benefits to which my child or I am entitled. If I decide to drop out, I should call Dr. Jin-Xiong She at 1-888-225-7785 or 706-721-4161. After withdrawing, no new information about my child will be collected, unless I allow it. I may refuse TEDDY's request to continue annual contact to ask about my child's health. Information about my child that was obtained before I dropped out may be used, but my child's name will never be attached to the information.

Can the Principal Investigator withdraw my child from this research study?
My child may be taken out of the study if he or she does not meet the study requirements or if the investigators think study participation would be harmful to my child or me. The National Institutes of Health is paying for the study. It can stop the study at any time.

Who will have access to my child's study records?
Only the investigator, the members of the research team, the sponsor (the National Institutes of Health), authorized officials from state and federal governments and accrediting bodies, and authorized representatives of the Medical College of Georgia or MCG Health, Inc., will have access to confidential data which would identify your child unless specifically required to be disclosed by state or federal law.

HAC FILE # 04-05-380
HAC APPROVED INFORMED CONSENT DOCUMENT
APPROVAL FROM 05/24/07 TO 05/23/08
THIS DOCUMENT IS NO LONGER VALID TO ENROLL SUBJECTS AFTER THIS DATE.

TEDDY ICD, Part I
Created 5/6/04, revised 7/8/04, 12/17/04, 5/15/06

Initials_____

Subject's name_____

Privacy Notice

The researchers are asking for my written authorization before using my child's or my health information or sharing it with others in order to conduct the research as described. However, under certain circumstances, the researchers may use and disclose my child's or my health information without my written authorization if they obtain approval through a special process to ensure that research without my written authorization poses minimal risk to my child's or my privacy. Under no circumstances, however, would the researchers allow others to use my child's or my name or identity publicly.

The researchers may also disclose my child's or my health information without my written authorization to people who are planning a future research project, so long as any information identifying my child or me does not leave our facility.

Authorization to Use and Disclose Health Information

If I sign this document, I give permission to all health care providers and researchers at MCG/MCGHI to use or disclose (release) my child's and my health information that identifies us for the research study described above. The health information that the investigators may use or disclose (release) for this research includes all information collected during the research described in this informed consent document and all protected health information (PHI) in my child's and my medical records that is related to the research. PHI from my child's and my medical records may include items such as laboratory reports, physician notes, nursing notes, radiology reports and other items related to our medical care. This information will be used to assess your child's health and understand what factors might play a role in contributing to type 1 diabetes or autoimmunity. The health information listed above may be used by and/or disclosed (released) to all investigators and team members involved with the research described above.

MCG/MCGHI is required by law to protect my child's and my health information. By signing this document, I authorize MCG/MCGHI to use and/or disclose (release) our health information for this research. Those persons who receive our health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share our information with others without my permission, if permitted by laws governing them. I do not have to sign this Authorization and informed consent document, but if I do not, my child will not be allowed to participate in the research.

I may change my mind and revoke (take back) this Authorization at any time, except to the extent that MCG/MCGHI has already acted based on this Authorization. To revoke this Authorization, I must write to Jin-Xiong She, Ph.D. 1120 15th St., CA-4124, Augusta, GA 30912-2400. If I revoke this Authorization, my child may no longer be allowed to participate in this research. Furthermore, even if I revoke this Authorization, the researchers may still use and disclose health information they already have obtained as necessary to maintain the reliability of the research. My child's protected health information is being collected and maintained as part of a database or data repository and, therefore, this Authorization will expire at the end of the research study. This study is expected to last almost 20 years. I will be allowed access to my child's PHI related to the study every 5 years.

HAC FILE # 04-05-380
HAC APPROVED INFORMED CONSENT DOCUMENT
APPROVAL FROM 05/24/07 TO 05/23/08
THIS DOCUMENT IS NO LONGER VALID TO ENROLL SUBJECTS AFTER THIS DATE.

TEDDY ICD, Part I
Created 5/6/04, revised 7/8/04, 12/17/04, 5/15/06

Initials_____

Subject's name_____

Consent To Collect And Store Samples For Future Research

Dr. She would like to store some of my child's leftover samples. If I agree, Dr. She will keep the samples in a specimen bank so that they may be used in future research to learn more about diabetes and other medical problems. Even if the research that is done on the blood cannot be used to help my child, it might help other people who have diabetes or other medical problems.

Please review the following statements and circle the right answers.

1. I agree that my child's left-over blood sample may be used by Dr. She or another qualified investigator for research to answer other medical questions that are not necessarily related to T1DM. Such studies will have approval from the Institutional Review Board before starting.

   YES NO Initials_____

2. I agree that Dr. She (or his designee) can contact me in the future to ask me to take part in more research. Such studies will have approval from the Institutional Review Board before starting.

   YES NO Initials_____

Signatures

The risks and benefits to my child if my child does participate in this study have been explained. I am encouraged to and will have the chance to ask questions and these questions will be answered.

_____
Subject's Name (print)

_____ _____
*Parent or Guardian's Name (print) *Parent or Guardian's Signature Date

*The individual above verifies that he/she is the natural parent and/or legal guardian of the above subject and as such has the legal authority to consent to the study outlined above.

_____ _____ OR ☐ Witness not available
Signature of Witness to the informed consent process (if available) Date

HAC FILE # 04-05-380
HAC APPROVED INFORMED CONSENT DOCUMENT
APPROVAL FROM 05/24/07 TO 05/23/08
THIS DOCUMENT IS NO LONGER VALID TO ENROLL SUBJECTS AFTER THIS DATE.

Initials_____

Subject's name_____

INVESTIGATOR STATEMENT:
I acknowledge that I have discussed the above study with this participant's parent or guardian and answered all of his/her questions. They have voluntarily agreed to participate. A copy of this document will be given to the subject or the subject's legally authorized representative.

_____
Printed name of investigator obtaining consent

_____ _____
Signature of investigator obtaining consent Date

HAC FILE # 04-05-380
HAC APPROVED INFORMED CONSENT DOCUMENT
APPROVAL FROM 05/24/07 TO 05/23/08
THIS DOCUMENT IS NO LONGER VALID TO ENROLL SUBJECTS AFTER THIS DATE.

Initials_____

IRB# 311-04

Informed Consent to Participate in Research and Authorization for Collection, Use, and Disclosure of Protected Health Information

University of Florida
Health Center
Institutional Review Board
APPROVED FOR USE
From 7/21/06 Through 7/20/07

You are being asked to take part in a research study. This form provides you with information about the study and seeks your authorization for the collection, use and disclosure of your protected health information necessary for the study. The Principal Investigator (the person in charge of this research) or a representative of the Principal Investigator will also describe this study to you and answer all of your questions. Your participation is entirely voluntary. Before you decide whether or not to take part, read the information below and ask questions about anything you do not understand. If you choose not to participate in this study you will not be penalized or lose any benefits to which you would otherwise be entitled.

If you are a parent, as you read the information in this Consent Form, you should put yourself in your child's place to decide whether or not to allow your child to take part in this study. Therefore, for the rest of the form, the word "you" refers to your child.

If you are a child or adolescent reading this form, the word "you" refers to you.

1. **Name of Participant ("Study Subject")**

_____

2. **Title of Research Study**

Consortium for Identification of Environmental Triggers.
Triggers and Environmental Determinants of Diabetes in the Young [TEDDY]. Part I. Screening

3. Principal Investigator and Telephone Number(s)

Desmond Schatz, MD
Professor & Associate Chairman
Dept. of Pediatrics
(352) 392-0330

Co-Investigator(s):

Dr. Janet Silverstein
Dr. Michael Haller

Research Coordinator:

Angie Choate
Dept. of Pediatrics
(352) 334-0843
toll free (800) 749-7424 ext. 334-0843

Research Nurses:

Roberta Cook
(352) 334-0857

4. Source of Funding or Other Material Support

National Institutes of Health, USA

5. What is the purpose of this research study?

Your child is being asked to join a study to help determine what causes type 1 diabetes mellitus (T1DM). T1DM used to be called childhood diabetes or insulin-dependent diabetes. T1DM occurs when special cells in the body, called the beta cells of the pancreas, are destroyed by the body's infection fighting cells, called immune cells. When these beta cells are destroyed, the body can not make insulin. Insulin is needed for the body to absorb the nutrients in food . Insulin helps keep the sugar level in the blood normal. If there is no insulin in the body, the sugar in the blood becomes too high and this makes someone get sick. When a child develops T1DM, they must take insulin shots every day to stay well.

Research tells us that children who get diabetes have a certain kind of gene. Other children who have this gene are at "high-risk" for getting diabetes. However, not all children who are high-risk get diabetes. We think that something happens that "triggers" or causes a child

with a high-risk gene to actually get diabetes. It is the purpose of this study to try and find out what are the triggers that cause children to get diabetes.

This study will look for children with this high-risk gene. Most children do not have a high-risk gene for T1DM. In the next phase of this study we hope to determine possible environmental factors that may cause T1DM.

We will have to study over 220,000 children to find enough with the high-risk gene. To find enough children, six places around the world have agreed to do this study

6a. What procedures would be done as part of your normal clinical care (even if you did not participate in this research)?

None.

6.b. What procedures will be done only because you are participating in this research study?

You are being asked to allow your baby to take part in this research study. We will take a tube of blood from the cord that is thrown out after the baby is born. Or, we will stick your baby's heel or finger to get 2-3 drops of blood. The law requires newborn's blood to be tested for certain diseases. We will get our blood at the same time so the baby does not have to be stuck twice. We will ask you who has diabetes in your immediate family.

Your child's blood will be sent to a laboratory. The laboratory will test the blood to see if your baby has a certain kind of gene. We are looking for babies who have the high-risk gene for T1DM.

If your baby does not have a high-risk gene for T1DM, you will receive a letter from us stating that. If your baby does have a high-risk gene, we will call you within 12 weeks. Your baby could then be enrolled, with your separate consent, in the second part of our research study. We will follow babies with the high-risk gene to see why some babies get T1DM and others do not. We will be looking for possible environmental factors leading to the development of T1DM.

If you have any questions now or at any time during the study, you may contact the Principal Investigator listed in #3 of this form.

7. If you choose to participate in this study, how long will you be expected to participate in the research?

Till study end – up to 15 years potentially.

8. How many people are expected to participate in this research?

220,000 in all sites, nationally and internationally.

9. What are the possible discomforts and risks?

If we get blood from the cord, your baby will feel nothing. If the blood comes from a heel stick or a finger stick, the baby may cry. There could be a bruise or swelling or infection. The risk of infection is small.

If your child has a high-risk gene for T1DM, you may feel worried or stressed. Some people worry that a person with a high-risk gene might be denied health insurance or life insurance. To protect your baby, we will not tell anyone else about your baby's genes. We will keep your baby's genetic information in locked files. Your baby will be given a number so names will not be used. Only members of the TEDDY study team will be able to use the locked files. No information will be put in your child's medical record by the study personnel. You may want to talk about the study with your child's physician. However, we suggest study information not be placed in your child's medical record.

This study may include risks that are unknown at this time.

Participation in more than one research study or project may further increase the risks to you. Please inform the Principal Investigator (listed in #3 of this consent form) or the person reviewing this consent with you before enrolling in this or any other research study or project.

Throughout the study, the researchers will notify you of new information that may become available and might affect your decision to remain in the study.

If you wish to discuss the information above or any discomforts you may experience, you may ask questions now or call the Principal Investigator or contact person listed on the front page of this form.

10a. What are the possible benefits to you?

If your baby has a high-risk gene for T1DM, your baby could be followed in Part 2 of the study. We would also tell you any new information we learn about what causes T1DM. We would tell you about any studies to prevent diabetes that might be right for your child. If your child got T1DM, we might diagnose it quicker, before he/she gets very sick. We would tell you about any studies for children with newly diagnosed T1DM.

10b. What are the possible benefits to others?

The results of this study will help us understand why some children with the high-risk gene get T1DM while other children with the same gene do not. When we understand this, we can try to prevent the disease

11. If you choose to take part in this research study, will it cost you anything?

No.

12. Will you receive compensation for taking part in this research study?

You will not be paid for taking part in this study

13. What if you are injured because of the study?

If you experience an injury that is directly caused by this study, only professional medical care that you receive at the University of Florida Health Science Center will be provided without charge. No other compensation is offered. Please contact the Principal Investigator listed in Item 3 of this form if you experience an injury or have any questions about any discomforts that you experience while participating in this study.

14. What other options or treatments are available if you do not want to be in this study?

You are free not to participate in this study. If you choose to participate, you are free to withdraw your consent and drop out at any time without this decision affecting your medical care.

15a. Can you withdraw from this research study?

You are free to withdraw your consent and to stop participating in this research study at any time. If you do withdraw your consent, there will be no penalty, and you will not lose any benefits you are entitled to.

If you decide to withdraw your consent to participate in this research study for any reason, you should contact Angie Choate at (352) 334-0843.

If you have any questions regarding your rights as a research subject, you may phone the Institutional Review Board (IRB) office at (352) 846-1494.

15b. If you withdraw, can information about you still be used and/or collected?

If you drop out of the study, we will not collect any more information from you or your child, unless you allow us to contact you annually to ask a few questions about the health of your child. Information we got before you dropped out may be used, but your child's name will never be used

15c. Can the Principal Investigator withdraw you from this research study?

You may be withdrawn from the study without your consent for the following reasons:

- Your child may be taken out of the study if he or she does not meet the study requirements.
- Your child may be taken out of the TEDDY study if the team thinks the study would do your child harm.
- The National Institutes of Health is paying for the study. It can stop the study at any time.

16. If you agree to participate in this research study, the Principal Investigator will create, collect, and use private information about you and your health. Once this information is collected, how will it be kept secret (confidential) in order to protect your privacy?

Information collected about you and your health (called protected health information), will be stored in locked filing cabinets or in computers with security passwords. Only certain people have the legal right to review these research records, and they will protect the secrecy (confidentiality) of these records as much as the law allows. These people include the researchers for this study, certain University of Florida officials, the hospital or clinic (if any) involved in this research, and the Institutional Review Board (IRB; an IRB is a group of people who are responsible for looking after the rights and welfare of people taking part in research

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to show information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government or the University of Florida that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

A Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Even with the Certificate of Confidentiality, the investigators continue to have ethical and legal obligations to report child abuse or neglect and to prevent you from carrying out any threats to do serious harm to yourself or others. If keeping information private would immediately put you or someone else in danger, the investigators would release information to protect you or another person.

.If you participate in this research study, the researchers will collect, use, and share your protected health information with others. Items 17 to 26 below describe how this information will be collected, used, and shared.

17. If you agree to participate in this research study, what protected health information about you may be collected, used and shared with others?

Your protected health information may be collected, used, and shared with others to determine if you can participate in the study, and then as part of your participation in the study. This information can be gathered from you or your past, current or future health records, from procedures such as physical examinations, x-rays, blood or urine tests or from other procedures or tests. This information will be created by receiving study treatments or participating in study procedures, or from your study visits and telephone calls. More specifically, the following information may be collected, used, and shared with others:

- Family history of T1DM(whether a first or second degree relative and age diagnosed)
- Your child's genetic test results
- Laboratory and other test results
- Diaries and questionnaires

If you agree to be in this research study, it is possible that some of the information collected might be copied into a "limited data set" to be used for other research purposes. If so, the limited data set may only include information that does not directly identify you. For example, the limited data set cannot include your name, address, telephone number, social security number, or any other photographs, numbers, codes, or so forth that link you to the information in the limited data set. If used, limited data sets have legal agreements to protect your identity and confidentiality and privacy.

18. For what study-related purposes will your protected health information be collected, used, and shared with others?

Your protected health information may be collected, used, and shared with others to make sure you can participate in the research, through your participation in the research, and to evaluate the results of the research study. More specifically, your protected health information may be collected, used, and shared with others for the following study-related purpose(s):

The study will try and find out why some children with the high-risk gene get T1DM and other children do not.

Your protected health information will be collected until the end of the study. If you have agreed to have your blood stored this information will be used and disclosed forever since it will be stored for an indefinite period of time in a secure database. If you remove your permission for the use and disclosure of your protected health information, then your information will be removed from the database.

19. Who will be allowed to collect, use, and share your protected health information?

Your protected health information may be collected, used, and shared with others by:

- the study Principal Investigator Dr. Desmond Schatz and his staff
- other professionals at the University of Florida or Shands Hospital that provide study-related treatment or procedures
- the University of Florida Institutional Review Board
- General Clinical Research Center

20. Once collected or used, who may your protected health information be shared with?

Your protected health information may be shared with:

- the National Institutes of Health which is paying for the study
- Government agencies responsible for overseeing research. These agencies may include the Food and Drug Administration, the Department of Health and Human Services, and the Office of Human Research Protections
- Government agencies responsible for overseeing public health. These agencies may include the Centers for Disease Control and Federal, State and local health departments
- TEDDY researchers

21. If you agree to participate in this research, how long will your protected health information be used and shared with others?

Your protected health information will be collected until the end of the study. If you have agreed to have your blood stored this information will be used and disclosed forever since it will be stored for an indefinite period of time in a secure database. If you remove your permission for the use and disclosure of your protected health information, then your information will be removed from the database.

22. Why are you being asked to allow the collection, use and sharing of your protected health information?

Under a new Federal Law, researchers cannot collect, use, or share with others any of your protected health information for research unless you allow them to by signing this consent and authorization.

23. Are you required to sign this consent and authorization and allow the researchers to collect, use and share with others your protected health information?

No, and your refusal to sign will not affect your treatment, payment, enrollment, or eligibility for any benefits outside this research study. *However, you cannot participate in this research unless you allow the collection, use and sharing of your protected health information by signing this consent/authorization.*

24. Can you review or copy your protected health information that has been collected, used or shared with others under this authorization?

You have the right to review and copy your protected health information. However, you will not be allowed to do so until after the study is finished.

25. Is there a risk that your protected health information could be given to others beyond your authorization?

Yes. There is a risk that information received by authorized persons could be given to others beyond your authorization and not covered by the law.

26. Can you revoke (cancel) your authorization for collection, use and sharing with others of your protected health information?

Yes. You can revoke your authorization at any time before, during, or after your participation in the research. If you revoke, no new information will be collected about you. However, information that was already collected may still be used and shared with others if the researchers have relied on it to complete and protect the validity of the research. You can revoke your authorization by giving a written request with your signature on it to the Principal Investigator.

27. How will the researcher(s) benefit from your being in this study?

In general, presenting research results helps the career of a scientist. Therefore, the Principal Investigator may benefit if the results of this study are presented at scientific meetings or in scientific journals.

28. **Signatures**

As a representative of this study, I have explained to the participant the purpose, the procedures, the possible benefits, and the risks of this research study; the alternatives to being in the study; and how the participant's protected health information would be collected, used and shared with others:

_____

Signature of Person Obtaining Consent and Authorization Date

You have been informed about this study's purpose, procedures, possible benefits, and risks; the alternatives to being in the study; and how your protected health information will be collected, used and shared with others. You have received a copy of this Form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask other questions at any time.

You voluntarily agree to participate in this study. You hereby authorize the collection, use and disclosure of your protected health information as described in sections 17-26 above. By signing this form, you are not waiving any of your legal rights.

Parent/Adult Legally Representing the Subject. By signing this form, you voluntarily give your permission for the person named below to be in this study. You are not giving up any legal rights for yourself or the person you are legally representing. After your signature, please print your name and your relationship to the subject.

_____

Signature of Parent/Legal Representative Date

_____

Print: Name of Legal Representative of and Relationship to Participant:

CONSENT TO COLLECT AND STORE TISSUE FOR FUTURE RESEARCH WHEN IDENTITY OF SUBJECT IS CODED AND THE CODES ARE KEPT IN LOCKED FILES BY THE PERSON CONDUCTING THE RESEARCH

As part of the research project Consortium for Identification of Environmental Triggers. Triggers and Environmental Determinants of Diabetes in the Young [TEDDY]. Part I. Screening Dr. Desmond Schatz would like to store some of your blood tissue that is not needed for your medical treatment and that would otherwise be thrown away. If you agree, Dr. Schatz will keep the samples in a specimen bank so that they may be used in future research to learn more about diabetes and other medical problems. Researchers are trying to learn more about diabetes, such as what causes diabetes, how to prevent it, how to treat it better, and how, hopefully, to cure it. Even if the research that is done on your tissue cannot be used to help you, it might help other people who have diabetes or other medical problems.

Many medical problems may arise due to the environment or from genetic factors. Diabetes may come from one or both of these causes. Genetic factors are those that people are born with and that can affect other family members. There may be genetic testing done in the future that would provide information about traits that were passed on to you from your parents or from you to your children. Dr. Desmond Schatz

Dr. Schatz or his successor will be responsible for making sure that your samples are protected in the specimen bank and that your medical information is kept confidential. Your samples will not be stored with your name or other identifying information but instead will be given a code number to protect your identity. The samples and this code number will only be given to researchers whose research is approved by the Institutional Review Board (IRB). (An IRB is a group of people who are responsible for looking after the rights and welfare of people taking part in research). The researchers will not be told who you are. Because the nature and value of any future research cannot be known at this time, any results obtained from using your tissue will not be given to you or your doctor.

The people who use your samples to do research may need to know more about your health. If researchers ask for reports about your health (information from your medical records), Dr. Schatz will not give them or anyone else your name, address, or phone number (unless you are willing to be contacted in the future to take part in more research). Although every effort will be made to keep your information confidential, there is a small risk that an unauthorized person may review your information. Therefore, there is a very slight risk that a test result could be linked to your identity and inadvertently disclosed to you or to a third party. If you were to receive the result of a genetic test that indicated a problem, it could cause anxiety or other psychological distress. In addition, you might have to decide whether or not to discuss the findings with members of your family. If a third party (like your employer or insurer) learned the results, there is a risk of discrimination that could affect your employability or insurability, of stigma, and of the unpredicted disclosure of this information to others. You can discuss these issues further with your doctor or nurse and you can request a consultation with a genetic counselor if you wish to discuss these possible risks. In addition, there are laws that require that research records that have your name on them may be shown to people who make sure that the research is being done correctly. As mentioned in the accompanying consent form, the NIH, FDA, and the Institutional

Review Board have the legal right to review and copy your medical records related to this research.

There will be no cost to you for any specimens collected and stored in the blood specimen storage bank. Your tissue will be used only for research and will not be sold. Some new products might be made because of the results of the research that uses your samples. These products might be sold sometime in the future, but, should this occur, you will not get paid.

The choice to let Dr. Schatz keep your tissue for doing research is entirely up to you. No matter what you decide to do, it will not affect your care. If you decide that your tissue can be kept for research but you later change your mind, tell Dr. Schatz who will remove and destroy any of your tissue that he still has. Otherwise, the samples may be kept until they are used up, or until Dr. Schatz decides to destroy them.

Please review statements 1, 2, 3, and 4 and then circle the answer that is right for you. If you have questions, please talk to your doctor or nurse.

1. I agree that my samples may be stored, coded to protect my identity, and that my identity will not be disclosed to anyone without my permission, except when required by law.

YES NO Initials_____

2. I agree that some excess blood tissue may be kept by Dr. Schatz for use in future research to learn about, prevent, treat, or cure diabetes.

YES NO Initials_____

3. I agree that my blood tissue may be used for research to answer other medical questions that are not necessarily related to diabetes.

YES NO Initials_____

4. I agree that my doctor (or someone he/she chooses) can contact me in the future to ask me to take part in more research.

YES NO Initials_____

C5. Site Specific Screening Informed Consents: Sweden

TILL BLIVANDE FÖRÄLDRAR

NI inbjuds att i samband med ert barns födelse delta i TEDDY-studien!

TEDDY-studien är ett forskningsprojekt som handlar om *diabetes hos barn*. TEDDY är en förkortning av The Environmental Determinants of Diabetes in the Young eller på svenska *Omgivningsfaktorers betydelse för uppkomst av diabetes hos barn.* TEDDY avlöser DiPiS-studien (DiabetesPrediktion I Skåne) och vänder sig också till *alla familjer i Skåne med ett nyfött barn.* Alla barn som föds på någon av de fem förlossningskliinikerna i Skåne kan vara med i TEDDY:s urvalsstudie. Att delta är helt frivilligt.

Under 4 år har DIPIS-studien samlat in blod från navelsträngen på 36.000 nyfödda barn i Skåne. Detta blod har undersökts för ärftlighet för diabetes. DiPiS följer upp ungefär 1/5 av dessa barn, som omfattar barn både med och utan förhöjd ärftlig risk. Deltagande barn lämnar varje år blodprov och föräldrarna fyller i frågeformulär med uppgifter om sådant som skulle kunna ha betydelse för utveckling av diabetes hos barn. DiPiS fortsätter parallellt med TEDDY, men inga nyfödda barn tas längre med i DiPiS-studien. Alla nyfödda barn erbjuds nu i stället att vara med i TEDDY:s urvalsstudie.

Varför delta i TEDDY?

Att vara med i TEDDY:s urvalsstudie innebär, liksom i DiPiS, att blod tas från barnets navelsträng i samband med förlossningen. I TEDDY får ni efter 2-3 månader besked om ert barns eventuella risk att få diabetes. Även om vi inte kan säga att ert barn aldrig skulle kunna få diabetes, kan vi ge besked om barnet har liten risk eller förhöjd risk att få diabetes. Många föräldrar tycker säkert det är bra att få veta att deras barn har liten ärftlig risk att utveckla diabetes. Föräldrar som får besked om att deras barn har förhöjd ärftlig risk kan bli ledsna och oroliga för sitt barn, men barnet kommer att kunna följas upp i TEDDY-studien. De allra flesta barn med förhöjd risk för diabetes får aldrig sjukdomen. Om barnet skulle få diabetes kan den förmodligen upptäckas tidigare och innan barnet blir riktigt sjukt. En tidig diagnos av barndiabetes är en fördel för barnet även på längre sikt. Om studier för att förhindra diabetes skulle starta kommer ni att få veta det och om det skulle vara lämpligt för ert barn att vara med i en sådan studie. Resultaten av TEDDY-studien kommer att hjälpa oss att få veta varför vissa barn får diabetes, medan andra inte får sjukdomen, trots att de har samma ärftliga risk.

Diabetes – en vanlig kronisk sjukdom hos barn

Diabetes hos barn kallas ibland barndiabetes, insulinberoende diabetes eller Typ 1 diabetes. Typ 1 diabetes är en av de vanligaste kroniska sjukdomarna hos barn. I Sverige drabbas fler än 600 barn per år och antalet barn som blir sjuka ökar, speciellt bland små barn. Sjukdomen uppstår då betacellerna i bukspottskörteln förstörs av kroppens eget immunförsvar. Betacellerna gör insulin. När de förstörs kan kroppen inte längre producera insulin. Insulin behövs för att kroppen ska kunna tillgodogöra sig mat och hjälper till att hålla blodsockret på rätt nivå. Om kroppen inte har tillräckligt med insulin blir blodsockernivån för hög och individen blir sjuk. Ett barn med diabetes, måste ta sprutor med insulin flera gånger varje dag för att må bra. Det finns ännu ingen bot för diabetes utan den som fått insulinberoende diabetes måste ta insulinsprutor under resten av livet.

Forskningen har lärt oss att de som får diabetes har ärftliga anlag för sjukdomen. Barn med ärftliga anlag har därför större risk att få diabetes än barn utan sådana anlag. Som tur är får långt ifrån alla barn diabetes trots att de har denna ärftliga risk. Man tror därför att något som finns i barnets miljö eller något som händer barnet "utlöser" eller orsakar att barnet faktiskt får sjukdomen. Syftet med TEDDY-studien är att försöka ta reda på vad det är för faktor eller faktorer som framkallar typ 1 diabetes.

Studie i två steg

TEDDY-studien genomförs i två steg. I steg 1 väljs de barn ut som sedan erbjuds vara med i steg 2 - uppföljningen. De flesta deltar endast i steg 1.

I samband med förlossningen tillfrågas ni om ni vill vara med i den första delen av TEDDY-studien. Om ni samtycker till att delta med ert barn, fyller man ett provrör med blod från ert nyfödda barns navelsträng och tar ett blodprov från mamma. Att ta blod från barnets navelsträng påverkar inte barnet på något sätt. Man tar blodprov på alla mammor som föder barn så det blir inget extra stick för TEDDY.

Att delta i steg 1 av TEDDY-studien innebär

- *att blod tas från barnets navelsträng,*
- *att ett blodprov tas på mamman i samband med barnets födelse,*
- *att föräldrarna inom 12 veckor får besked om barnet har förhöjd risk för typ 1 diabetes eller ej och*
- *att blodproven avidentifieras om barnet inte har förhöjd ärftlig risk.*

Blodproven skickas till Universitetssjukhuset MAS i Malmö. Där undersöks blodet från barnets navelsträng för ärftlighet för typ 1 diabetes. Mammans blod sparas och kommer bara att användas om barnet skulle ha förhöjd risk. Ungefär 7 av 100 födda barn har denna förhöjda risk. Om ert barn inte har förhöjd ärftlig risk för typ 1 diabetes kommer ni att meddelas detta per brev. Er medverkan i TEDDY-studien är då avslutad och blodproven från mamma och barn avidentifieras genom att namn och personnummer tas bort från proverna.

Uppföljning

TEDDY-studiens steg 2 är uppföljning. Om vi finner att ert barn har en *förhöjd ärftlig risk* att utveckla diabetes, kontaktar vi er per telefon. Vi erbjuder er då att vara med i TEDDY-studiens uppföljning, som kommer att pågå under flera år framöver. I uppföljningen vill vi ta reda på varför endast en del barn med förhöjd ärftlig risk får typ 1 diabetes medan andra inte får sjukdomen. Vi vill följa barnen till dess de är 15 år. Under dessa år tar vi reda på en mängd olika saker om barnen som t.ex. vad barnen äter, vilka sjukdomar barnen får, vilka stressande faktorer eller andra livshändelser barnen eventuellt utsätts för m.m. Vi kan också med hjälp av blodprov se om barnet skulle visa tecken på diabetes. För att kunna göra detta kommer vi att behöva träffa föräldrar och barn med jämna mellanrum på en TEDDY-mottagning. Bl.a. vill vi ha blodprov från barnen och föräldrarna får besvara frågor. Samtidigt får ni föräldrar svar på era frågor och får hjälp och stöd från våra forskningssköterskor om ni skulle behöva det.

Helt frivilligt

Om ni erbjuds att delta i TEDDY-studiens andra del, får ni senare ge ert skriftliga samtycke till detta. Innan ni bestämmer om ni vill delta får ni utförlig information och svar på era frågor om vad ett sådant deltagande innebär. Eftersom TEDDY-studien är en långvarig studie kommer vi senare att också be barnet om dess samtycke till att vara med. Att delta i TEDDY-studien är helt frivilligt och föräldrar och barn kan ångra sitt deltagande när som helst.

Avidentifierade uppgifter

Vi kommer inte att informera någon utomstående om ert barn har förhöjd ärftlig risk eller ej. Uppgifter om ert barns ärftlighet förvaras i låsta skåp och i datafiler som endast några få av TEDDY:s personal har tillgång till. Alla forskningsresultat från TEDDY-studien redovisas endast som resultat från grupper. Uppgifter om enskilda individer kan aldrig spåras. TEDDY-studien är ett internationellt samarbetsprojekt mellan flera forskningscenter, men identiteten på svenska barn och resultaten på enskilda barns prov eller uppgifter om enskilda familjer lämnas inte ut till de övriga forskningscenter vi samarbetar med. I den gemensamma TEDDY-studien är varje barn/familj endast ett nummer.

Uppgifter om barns diabetesrisk lämnas inte ut till försäkringsbolag. Föräldrar har heller ingen skyldighet att ge sådan information. Alla föräldrar rekommenderas att försäkra sitt nyfödda barn vare sig man kan komma att vara med i någon del av TEDDY-studien eller inte.

Fakta om TEDDY-studien

Tre grupper av forskare från Europa (en i Sverige, Finland respektive Tyskland) och tre grupper i USA samarbetar i TEDDY. Alla dessa forskningsgrupper kommer att följa barn med förhöjd ärftlig risk för diabetes. Alla samlar in samma information om de barn som är med i studien. Tillsammans kommer vi att undersöka ärftligheten hos 220.000 barn för att finna tillräckligt många barn med förhöjd ärftlig risk. I Sverige är det en forskargrupp på Universitetssjukhuset MAS i Malmö som ansvarar för den svenska delen av TEDDY-studien. Huvudansvarig är Åke Lernmark, professor i diabetesforskning vid Lunds Universitet och Universitetssjukhuset MAS i Malmö. TEDDY-studien är godkänd av den regionala forskningsetiska kommittén vid Lunds Universitet.

Mer information om TEDDY

Mer information och svar på frågor om TEDDY-studien kan ni få av våra TEDDY-sköterskor eller av vår samordnande forskningssköterska. Ni kan också läsa om TEDDY-studien på TEDDY:s svenska hemsida www.xxxxxxxxxxxxxxxxx eller internationella hemsida: www.teddystudy.org.

Samordnande forskningssköterska:
Gertie Hansson tfn 040/332073; gertie.hansson@skane.se
Forskningsköterskor:

TEDDY

SAMTYCKE

Genom att skriva under detta formulär bekräftar jag följande:

- Att jag läst den skriftliga informationen om studien och fått studien muntligt förklarad för mig.
- Att jag haft möjlighet att diskutera studien med någon av TEDDY-studiens forskningssköterskor och att jag fått svar på mina frågor.
- Att jag förstår att mitt deltagande i studien är helt frivilligt och att jag när som helst kan avbryta mitt deltagande.
- Att jag ger mitt tillstånd till att blod får tas från mitt barns navelsträng och att detta blod får analyseras för ärftlig risk för typ 1 diabetes.
- Att ett blodprov får tas från mamman i samband med förlossningen.
- Att detta samtycke endast omfattar deltagande i urvalet till TEDDY-studien.

Mammas namn	Namnteckning	Datum

Mammas personnummer .....

Pappas namn	Namnteckning	Datum

Barnmorskans namn	Namnteckning	Datum

Förlossningsklinik eller mödravårdsmottagning

Barnets födelsedatum..... .....

Barnets TEDDY-nummer (6-siffror) .....

TEDDY

SAMTYCKE

Jag samtycker till att blod får tas från mitt nyfödda barns navelsträng. Jag samtycker också till att detta blod analyseras för ärftlig risk för typ 1 diabetes.

Mammas namn	Namnteckning	Datum

Mammas personnummer .....

Pappas namn	Namnteckning	Datum

Barnets födelsedatum..... .....

Barnets TEDDY-nummer (6-siffror) .....

Barnmorskans namn	Namnteckning	Datum

Förlossningsklinik eller mödravårdsmottagning

C6. Site Specific Screening Informed Consents: Washington

Pacific Northwest Research Institute

720 Broadway, Seattle, WA 98122

SCREENING CONSENT FORM (11f)

The Environmental Determinants of Diabetes in the Young- TEDDY Study

Researchers:

William Hagopian, M.D., Ph.D., Clinical Associate Professor of Med/Endocrinology 206-860-6759
Michael Brantley, EMTP, Clinical Research Coordinator, PNRI, 206-860-6770
Hui Peng, M.D., Ph.D., Senior Research Fellow, PNRI, 206-568-1481
Martha Horike-Pyne, BS, Clinical Research Coordinator, PNRI, 206-568-1485
Emily Wion, BA, Clinical Research Coordinator, PNRI, 206-568-1460
Jennifer Ugale, BS, Staff Researcher, PNRI, 206-568-1455
Kristen Hay, BA, Staff Researcher, PNRI, 206-860-6758
Claire Cowen, BA, Staff Researcher, PNRI, 206-860-6754
Christina Thylstrup, BS, Staff Researcher, PNRI, 206-726-1209
Sue LaFever, BA, Staff Researcher, PNRI, 206-726-1250
Viktoria Stepitova, MA, Staff Researcher, PNRI, 206-568-1469
Denise Mulenga, BS, Staff Researcher, PNRI, 206-860-6758
Carrie Mayer, MA, Staff Researcher, PNRI, 206-860-6758

Toll Free Number 1-888-324-2140 / Emergency 24-hour pager 206- 907-8802

RESEARCHERS' STATEMENT

We are asking your child to be in a research study. The purpose of this consent form is to give you information to help you decide whether you and your child should be in the study. Please read the form carefully. You may ask questions about the purpose of the research, what we would ask you and your child to do, possible risks and benefits, your child's rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions, you can decide if you and your child want to be in the study. This process is called 'informed consent'. We will give you a copy of this form for your records.

PURPOSE AND BENEFITS

Researchers at six centers around the world are studying possible environmental causes of type 1 diabetes. We know that about half the risk is due to environmental causes and about half to genetics. Since about 75% of the children who will develop diabetes have genetic markers, we are asking genetically at risk children to participate. We offer a diabetes risk-screening test for your baby that will show if s/he is at increased risk. Even if you have no family history of diabetes, you can help. If your baby is at increased risk for getting type 1 diabetes,

we will give you information about the disease. You also will be asked if you would enroll your child in a long-term study with future testing. There is no cure for diabetes yet. Participating in the screening or follow-up study cannot prevent type 1 diabetes in your child. However, your participation may help you identify and seek treatment earlier than you otherwise would in the event that your child develops the disease. This research may lead to greater knowledge of this disease that may help children in the future.

PROCEDURES

The state of Washington provides a Newborn Screening for several childhood illnesses for all children born in our state. This requires a heel stick to your baby where several drops of blood are collected on a card. We are working with the Washington State Newborn Screening Program to use a small bit of the leftover blood spot, if we have your written permission. We will not poke your baby an extra time to get a blood sample. We will ask you for contact information (name, address, phone number), general information about your child (hospital, date and approximate time of birth, birth weight, gender, race and ethnicity), and if there is any type 1 diabetes in your family. We will not need any of your medical records. We will test the blood spot for genetic risk for developing type 1 diabetes, and notify you of your child's test results within 4 months. Any blood spot left over after the genetic test will be destroyed and not used for any other purpose. The majority of parents will find that their child is not at increased risk for developing diabetes (95%). For these children, screening will provide reassuring results at no cost and with no extra sampling. About 5% of parents will find out their child is at increased risk for developing diabetes and will be informed about the follow-up study. If you do not wish to be told your child's test results, we suggest you do not participate in the study. The follow-up phase of TEDDY will look for environmental triggers of type 1 diabetes. This will include studying things like your child's diet, illnesses, allergies, and family stresses. If you agree to be in this follow up study, we will ask to see you and your child at the research clinic every three months. More detailed information and another consent form will be provided if your child is eligible for the follow-up study. We are only asking you to participate in a single screening test at this time.

RISKS, STRESS, OR DISCOMFORT

The testing for this study has no added medical risk for your child. Some parents may worry about their child's chance of getting type 1 diabetes. Some parents may find it hard to wait for test results. Some parents may treat their child differently because of this information. Study staff is available to discuss your concerns and answer any questions you may have about the study, the results,

or diabetes. If information about this study is put in your child's medical record, it might hurt your child's access to health insurance. We will keep all study data separate from the medical record. You are free to discuss this study with your physician, but we suggest the study information not be placed in your child's medical record. In addition, samples will be coded and we will maintain strict confidentially. We will protect your privacy and will only give results to the child's parent or legal guardian. Exceptions may be made to this promise of confidentiality only if child abuse and/or neglect are suspected. You may contact us toll free- 1-888-324-2140 or 24 hour pager at 206-907-8802 if you have any concerns.

OTHER INFORMATION

Being in this study is voluntary. There is no charge for this screening test or for any part of the research study. Your child's test results will be kept for 15 years. It will be coded and kept private in locked files, in a locked building. Only TEDDY study personnel, the National Institutes of Health, and the Washington State Institutional Review Board that oversees the rights and protection of human subjects will see your child's results. You are free to ask or refuse any question and/or withdraw from the research study at any time, for any reason, without any penalty, by contacting any of the investigators listed at the top of this consent form.

Your child's health records are considered protected health information. These health records can include your child's family history of T1DM and your child's genetic test results. Only members of the TEDDY study team and the Institutional Review Board have the legal right to see your research records. We will not show your research records to anyone without your permission.

When we talk about the study at scientific meetings, we will never use your name or your child's name. When we write about the study in scientific journals, we will never use your name or your child's name.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation

of Federally funded projects or for information that must be disclosed in order to meet the requirements of the Federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Even with the Certificate of Confidentiality, the investigators continue to have ethical and legal obligations to report child abuse or neglect and to prevent you from carrying out any threats to do serious harm to yourself or others. If keeping information private would immediately put you or someone else in danger, the investigators would release information to protect you or another person.

Department of Health and Human Services (DHHS) personnel may request identifying information for purposes of performing audits, carrying out investigations of DHHS grant recipients, or evaluating DHHS funded research projects.

SUBJECT'S STATEMENT

This study described above has been explained to me. I give my permission for the Washington State Newborn Screening Program to release a small portion of my child's blood spot to the TEDDY Study. I have been told that the blood spot will be tested by the researchers to find out whether my child has a higher than average risk of developing type 1 diabetes in the future. I have been told that I will be informed of the results of this test in about four months. I will be given a copy of this consent form. If I have questions about this study, I can contact one of the researchers listed on this form. If I have questions about my rights as a research subject, or about my child's rights as a research subject, I can call the Washington State Institutional Review Board at 1-800-583-8488.

_____
Printed name of subject

_____
Signature of parent

_____
Printed name of parent

APPROVED THROUGH
OCT 06 2007
Washington State
Institutional Review Board

_____
Date

INVESTIGATOR'S STATEMENT

To the best of my knowledge, the subject understands the study goals, and risks and benefits. The subject has had all questions satisfactorily answered. The subject has voluntarily agreed to release a portion of the Newborn Screening Program blood spot to this study that will only be used for genetic risk of developing type 1 diabetes. The subject understands all participation is voluntary. The subject received a copy of this consent.

_____

Signature of researcher

_____ _____

Printed name of researcher Date

D. Model Infant Screening Form

Date of Screening: ____/_____/_____ **Child's Date of Birth:** ____/_____/_____

Local Code: __ __ __ __ __ __ __ **Clinical Center:** __ __ __ **Visit Location Code:** __ __ __

TEDDY Staff Code: __ __ __ __ **Interviewer:** _____

Has the child's parent(s) or legal guardian(s) given signed informed consent for the child to be screened?
( ) No ( ) Yes

Child's Information:
Sex: ( ) Male ( )Female **Birth Number:** ( ) Singleton ( )Twin ( ) Triplet

Race:
(Check all that apply)
( ) White
( ) Black or African American
( ) Asian
( ) Native Hawaiian, or other Pacific Islander
( ) Native American, Alaskan Native, Aboriginal Canadian, Aboriginal Australian
( ) Unknown or not reported

Ethnicity:
Is this child of Hispanic, Latino, or Spanish origin?

( ) No
( ) Yes
( ) Unknown or not reported

Mother's Date of Birth: ____/_____/_____ **Father's Date of Birth:** ____/_____/_____

Family History of Type 1 Diabetes:
Does this child have any family members with Type 1 Diabetes? ( ) No ( ) Yes ( ) Unknown

If yes, who? (check all that apply) ( ) Mother ( ) Father ( ) Sibling

---

Study History:
Does this family have another child already enrolled in this study? ( ) No ( ) Yes

If "Yes" please provide child's Local Code: _____

Was the Mother involved in the pregnancy study? ( ) No ( ) Yes

If "Yes" please provide Mother's Local Code: _____

HLA Sample Information:
Sample draw date:

____/_____/_____
(DD/MMM/YYYY)

HLA screening sample number:

_____

Clinical Center Use Only:

Child's Name: (Last) _____ (First) _____ (MI) _____

Hospital of Birth: _____

Mother's Information:
Name: (Last) _____ (First) _____ (MI)_____

Father's Information:
Name: (Last) _____ (First) _____ (MI)_____

Primary Caretaker's Information:
Name: (Last) _____ (First) _____ (MI)_____

Contact Information of Primary Caretaker:

Address: _____

City: _____ State: _____ Zip: _____

Telephone number: (home)_____ (work) _____

Email: _____

E. MODEL SCREENING FREQUENTLY ASKED QUESTIONS

Q: What is HLA Screening?
A: Human Leukocyte Antigen (HLA) screening uses either whole blood cells or a gene to identify combinations of genes that have been found more often in children with T1D. HLA accounts for only about 50% of the genetic risk for developing T1D.

Q: What is Type 1 Diabetes?
A: The pancreas is an organ that lies just behind the stomach and has islet cells that produce a hormone called insulin. When the blood sugar rises after meals, the pancreas secretes insulin into the bloodstream. The insulin is necessary to transfer sugar from the blood into cells, where it is turned into energy for the needs of the whole body.

For some unknown reason, antibodies in the body can start attacking the pancreas until all the insulin producing cells are destroyed. Without insulin, the sugar is stuck in the blood and can't move into the other cells of the body, and the cells starve. The amount of sugar in the blood then rises, and glucose pours out of the body in the urine. Water and salts are lost with the glucose, the amount of urine increases, and the child is continuously thirsty. The child loses weight and becomes tired and lethargic. At this stage, treatment with insulin is needed immediately. A person with Type 1 diabetes must get insulin immediately and continue to take it throughout life. Without insulin, a person with diabetes can get very sick and die. However, with several daily insulin shots and monitoring of blood sugar levels, people with Type 1 diabetes can live normal lives.

Q: What is the difference between T1D and T2D?
A: Type 1 is also known as insulin-dependent or childhood diabetes and is an autoimmune disease. It typically happens in childhood or adolescence and almost never after age 35. The immune system inappropriately attacks the insulin producing cells until they are all gone. It is treated by injecting insulin and monitoring blood sugar levels. It is much less common than Type 2 Diabetes, which typically happens in overweight, older adults. Type 2 diabetes is not an autoimmune disease; insulin is still produced, it just doesn't work anymore. It is treated through diet and exercise, oral medications, and sometimes insulin injections.

Q: How many children in the general population are at higher risk for T1D?
A: In the United States, we expect to find approximately 5% of the children screened will be at higher risk for T1D.

Q: How many children with a first degree relative with T1D are at higher risk?
A: In the United States, we expect to find approximately 30% of the children screened will be at higher risk for T1D.

Q: How accurate are these genetic tests?
A: When TEDDY determines that your baby has the genes that increase his/her risk for developing T1D, we are more than 98% sure the genetic testing results are accurate. However, they cannot predict whether a person will get diabetes.

Q: What are TEDDY researchers looking for?
A: TEDDY is focused on searching for things in the environment that can start the diabetes process. We are collecting information about diet, viruses, medications, immunizations, pollutants and stress.

Q: How will this study benefit my child?
A: You can benefit by knowing what your child's risk for developing T1D is, and by learning what to look for. If your child does develop diabetes, participating may help with early diagnosis, which can lead to better treatment.

Q: Will my child's insurability be affected by these results?
A: No. By law, TEDDY results should not have any effect on your child's health insurance. These tests are for research only and are considered protected information that your insurer is not entitled to review. The predictive tests tell us whether or not your child is *at increased risk for* getting diabetes over a child who does not have these genes. They cannot predict diabetes with certainty. To avoid confusion, it is wise to avoid having any information about TEDDY on your child's hospital or doctors' medical charts.

Q: Will it cost me anything to participate?
A: No. TEDDY is funded by the National Institutes of Health, and will provide your child's testing for free. TEDDY may be able to help you with some of your travel costs for study visits.

6. SCREENING RESULTS NOTIFICATION

Notification of results will be the last step in the screening phase of the study. Among those determined to be eligible, notification will be the first step in recruitment into the follow-up TEDDY study (see MOO Section 7). The primary goals are: 1) to inform all subjects who participated in the genetic screening phase of the study of the results of screening and 2) among those eligible for follow-up, to further discuss the results of the genetic screening, describe the follow-up study, and invite them and their child to participate in the follow-up study. With the first visit being at 3-4 ½ months, the need to be attentive to the time course of this process is crucial. The timeline below marks critical points of contact.

Child's age in weeks

1	2	3	4-6	7	8-11	12	13	14	15	16	17	18
HLA Test			Results returned	Low Risk Notified	Start Contacts with Eligible High Risk	Continue enrollment process						
						Ideal time for 1st Visit						

6.1. HLA Lab Screening Reports

The local labs performing the cord-blood/heel stick HLA screening will return results to the clinical center and the DCC simultaneously. Results should ideally be returned within 4 weeks of birth. Receipt of results after subjects have reached 6 weeks of age will significantly reduce the time available to recruit and enroll eligible subjects (those at higher/increased risk). Results will be sent by the HLA laboratory to the clinical center and to the DCC, in the form of an Excel spreadsheet that indicates the PCR probe pattern and the HLA genotypes and haplotypes. The results will be imported by the DCC and the clinical center into a database, and a pre-determined algorithm will be used to independently classify genotypes and haplotypes based on the probe pattern. If the HLA genotypes and haplotypes assigned by the clinical center do not match those assigned by the HLA laboratory, the laboratory will be contacted to resolve the discrepancy.

The DCC will import results from the HLA laboratory and confirm eligibility status for each screened subject. A confirmatory email will also be sent to the clinical center. The DCC's report of eligibility status will be compared to that of the clinical center. If the eligibility status of the DCC and the clinical center for that infant do not match, the clinical center will contact the DCC to resolve the status.

i) HLA eligibility for general population infants

Infants from the general population are eligible for enrollment and long term follow-up if they:

- Have any one of the following HLA genotypes:
  a. DR4[&]-DQA1*030X-DQB1*0302[@] / DR3-DQA1*0501-DQB1*0201
  b. DR4[&]-DQA1*030X-DQB1*0302[@] / DR4[&]-DQA1*030X-DQB1*0302[@]
  c. DR4[&]-DQA1*030X-DQB1*0302[@] / DR8-DQA1*0401-DQB1*0402
  d. DR3-DQA1*0501-DQB1*0201 / DR3-DQA1*0501-DQB1*0201

[@]Acceptable alleles in this haplotype include both DQB1*0302 and *0304

[&]For general population subjects, DR4 subtyping must exclude DRB1*0403

Each extended haplotype listed above must be accurately identified, which usually requires allele typing at two or more of the three genes. For subjects indicated as DR4 above, DR4 subtyping must be used to identify DRB1*0403 for exclusion. Screening centers may use methods to identify DRB1*0403 for General Population exclusion which do or do not separately identify DRB1*0407. TEDDY will allow but not require DRB1*0407 subjects to be excluded from the General Population follow-up.

- Have a parent or primary caretaker who has given informed consent for surveillance enrollment.

Infants are excluded if:

- They have an illness or birth defect that precludes long-term follow-up or involves use of treatment that may alter the natural history of diabetes (e.g. steroids or insulin).

ii) **HLA Eligibility for Infants with a First-degree TID relative (FDR):**

- Have any one of the following HLA genotypes:
  a. DR4- DQA1*030X-DQB1*0302[@] / DR3- DQA1*0501-DQB1*0201
  b. DR4- DQA1*030X-DQB1*0302[@] / DR4- DQA1*030X-DQB1*0302[@]
  c. DR4- DQA1*030X-DQB1*0302[@] / DR8- DQA1*0401-DQB1*0402
  d. DR3-DQA1*0501-DQB1*0201 / DR3-DQA1*0501-DQB1*0201
  e. DR4- DQA1*030X-DQB1*0302[@] / DR4- DQA1*030X-DQB1*020X
  f. DR4- DQA1*030X-DQB1*0302[@] / DR1[#]- DQA1*0101-DQB1*0501
  g. DR4- DQA1*030X-DQB1*0302[@] /DR13-DQA1*0102-DQB1*0604
  h. DR4- DQA1*030X-DQB1*0302 / DR4- DQA1*030X-DQB1*0304
  i. DR4- DQA1*030X-DQB1*0302[@] / DR9- DQA1*030X-DQB1*0303
  j. DR3- DQA1*0501-DQB1*0201 / DR9- DQA1*030X-DQB1*0303

[@]Acceptable alleles in this haplotype include both DQB1*0302 and *0304

[#]In this DQB1*0501haplotype, DR10 (present in ~ 7% of DQB1*0501 haplotypes) must be excluded. Only DR1 is eligible.

- Each extended haplotype listed above must be accurately identified, which usually requires allele typing at 2 or more of the 3 genes. DR4 subtyping is not required for relatives.

- Have a parent or primary caretaker who has given informed consent for surveillance enrollment.

Infants are excluded if:

- They have an illness or birth defect that precludes long-term follow-up or involves use of treatment that may alter the natural history of diabetes (e.g. steroids or insulin).

6.2. DCC Result Reporting

Each local HLA screening lab will use the TEDDY website to upload files to the DCC, containing HLA results and eligibility status. The DCC will import these results into a database and a pre-determined algorithm will be used to independently classify genotypes and haplotypes based on the probe pattern. If the DCC detects an inconsistent eligibility status between the interpretation from the lab and that from the DCC, the local HLA lab will be notified of the inconsistency. Otherwise, the DCC will notify each clinical center, by email, of subjects that were deemed HLA eligible by both the HLA lab and the DCC, and those deemed ineligible by both the HLA lab and the DCC.

6.3. Results Notification Training

All TEDDY staff members engaged in direct contact with eligible families must be trained and practiced in results notification and details of the TEDDY follow-up study before contacting participants to notify them of the child's increased risk for TID. Training will occur initially at a centralized training session or at the local sites by approved trainers. Elements of the training will be the same across the life of the study and include:

i) Reading the Manual of Operations and the Protocol related to recruitment activities
ii) Participating in an interactive review of all elements of the recruitment process with a trainer or through observing this section of the centralized training video.
iii) Participating in practice sessions with mock subjects going through all the elements of the recruitment process as observer, as mock subject, and as recruiter. Observing selected video tapes of centralized training may be substituted, in part, for real life observation.
iv) Elements of this training will include communicating results to families, explaining the meaning of the results, educating parents about diabetes, describing the study and it's purpose, inviting parents to ask questions and being prepared to answer FAQs, inviting them to participate in the study, and scheduling their first visit.
v) Before being approved to begin recruitment all new staff must observe a trained recruiter (one-sided observation) performing all steps of the recruitment process with eligible families.
vi) Before being approved to begin recruiting activities solo, the recruiter will be observed by a trained recruiter (one-sided observation) performing all steps of the recruitment process with eligible families.

6.4. Low Risk HLA Results Notification

When the infant's HLA genetic test result indicates that the infant is NOT eligible for follow-up in TEDDY, a standard letter will be sent to the infant's mother or the person who signed the screening informed consent. The letter should state that:

1. The child's risk for diabetes is the same as the average child.
2. The result does not mean the child will never develop diabetes; do NOT provide numerical risk estimates for the "average" child.
3. Ask the participant to call if the child ever develops type 1 diabetes.

A model letter is included in Appendix A. Each site-specific letter is in Appendix B as well. Each notification letter will be generated by the clinical center; a copy will be filed at the clinical center and the original mailed to the person completing the screening informed consent.

6.5. High Risk HLA Results Notification

High Risk status will be confirmed with the DCC prior to any family contact. Parental notification of high-risk results should be done in person, by telephone, or face-to-face. Centers have the option of sending a postcard or letter by mail, indicating the baby's test results are available and asking the parent to call a toll-free number for the results, calling the parent directly with the results, or scheduling a face-to-face meeting where the results are explained. Once the results are explained to the parent, a follow-up letter confirming the test results should be sent home. It is recommended that the first contact with parents of a high risk infant not start until the child is at least 6 weeks old.

Centers that elect to notify the parents of the availability of test results by mail should send this information in an envelope to protect private health information to the person who provided informed consent for the baby's blood to be tested. Although this can be site specific in format, a stock weight paper in bright color, with TEDDY logos is suggested. A recommended script is provided in the Appendix C. A tracking sheet (sample provided in Appendix D) should be printed that lists the parent's (or person who consented to the baby' blood test) name, child's name and date of birth, address and phone number as well as an area to write down contact information (e.g., dates letter sent home, dates of efforts to contact by parent by phone, etc). If the parent (or person who consented to the baby's blood test) does not call within one week, TEDDY staff will begin to try to contact the parent by phone.

6.5.1. Discussing High Risk HLA Results

Parental notification of high-risk results should be done in person, by telephone or face-to-face. There are several objectives to be met in this contact or series of contacts, and it is important not to overwhelm the parent with information. The objectives for this conversation are:

- Informing the parent of the child's higher risk for type 1 diabetes (specific to general population and FDR risks)
- Re-stating this information in a letter sent home
- Giving parents time to digest this information and to ask questions
- Explaining a bit about diabetes at a level appropriate to their prior knowledge (i.e. FDR parents may be more familiar with diabetes and may need less information)
- Explaining TEDDY and inviting them to participate in the follow-up study
- Explaining the details of what would be involved in participating with TEDDY

It is important to note that this information could be very distressing to parents. It is a conversation that is with someone they have never met, for a test they may have forgotten that they had done, and it is about their new baby who is only 6-8 weeks old. Available research indicates that the results are better understood if a follow-up letter is sent home re-stating the information provided in the initial contact. Model letters are provided in the

Appendix H-K. Experience suggests that these results are better understood and considered by the parents after the child is at least 6, and preferably after 8 weeks of age. Clinical centers may want to take this into account when planning the contact schedule and steps with these eligible families. It is also possible that in talking with one parent (frequently the mother) the recruiter will find that this parent will want to talk everything over with their spouse. For this reason the recommended approach to the results notification and enrollment contacts is to have this process occur over 2 calls and a mailing.

A recommended script for the initial contact is provided in Appendix E for General Population families and Appendix F for First Degree Relative families. A telephone message script is provided in Appendix G.

6.5.1.1. Recommended sequences for high-risk HLA results notification and invitation to enroll in follow-up:

Although the content of the information given parents of high-risk children will be similar across sites, sites will vary in how this information is delivered. A recommended sequence for high-risk HLA results notification and invitation to enroll in TEDDY is presented below. Each site will provide to the DCC the specifics of its high-risk HLA results notification and invitation for enrollment plan.

(i) The TEDDY staff explains the child's HLA results to the parent by telephone and reviews information about diabetes with the parent, invites questions, and ends with a brief description of TEDDY and asking whether they would consider enrolling. The TEDDY staff describes materials to be sent home for parents to review and arranges a time for further discussion (by phone or in-person) about enrolling in the follow-up portion of the study.

(ii) Material to be sent:

- Results letter
- Study Brochure
- Information outlining requirements for each visit
- General information about diabetes (see Appendix Q)
- FAQs (see Appendix R)

(iii) Arrange and conduct a follow-up phone call or in-person meeting where the TEDDY study is further described, questions about the study are invited, and the enrollment decision is sought.

6.5.1.2. Failure to Contact Parent with High-Risk HLA Results

Each site will make every effort to contact the baby's parent to provide the high-risk HLA results in person. Each contact attempt will be recorded and each will specify how many contacts will be attempted before the effort is closed. Clinical centers may elect or be required by their IRBs to inform the parents of the high risk result in a letter if a personal contact has not been made where the result is communicated. This letter should only contain the statement that their child was found to have the higher risk genes and should not contain risk numbers. Site specific letters are provided in Appendix P.

Centers electing to notify this group of parents in writing should be attentive to the time course. The timing is important if the study wants to provide the opportunity for parents to decide to participate within a time frame that meets the latest date a child can be enrolled in the follow-up study (4 ½ months old). If a letter is sent when the child is between 14 and 15 weeks of age, this will allow 2 weeks in which to schedule a visit for those parents who, upon getting the result, decide they want to participate.

If a center elects not to send a final results letter to parents who have not had a personal contact and elects to leave a final voice message a model telephone message script, preserving the privacy of medical information, is provided in the Appendix.

Ideally a child will be scheduled for the first visit close to 12 weeks of age. Once the child is 18 weeks old, the baby is no longer eligible for TEDDY.

Section 6 –Appendix

A. Model Low Risk Letter
B. Site Specific Low Risk Letters
    1. Colorado (General Population and FDR)
    2. Germany (General Population and FDR)
    3. Georgia/Florida
    4. Sweden
    5. Washington
    6. *Finland gave a brochure to everyone at hospital; does not send a letter*
C. Model letter/postcard for Higher Risk Subjects To Notify That Results Are Available.
D. Model Call Tracking Sheet
E. Model Script For Initial Telephone Contact to Explain High Risk HLA Results to General Population Families – US Sites
F. Model Script For Initial Telephone Contact to Explain High Risk HLA Results to Families with First Degree Relatives with Type 1 Diabetes– US Sites
G. Model Telephone Message Script
H. Model Follow-up Letter Re-Stating Child's HLA Results for General Population Parents Considering Participation in TEDDY
I. Site Specific Follow-up Letters Re-Stating Child's HLA Results for General Population Parents Considering Participation in TEDDY
    1. Colorado
    2. Germany
    3. Georgia/Florida
    4. Washington
    5. *Sweden informs over the phone; does not send a letter*
    6. *Finland gave a brochure to everyone at hospital and informs over the phone; does not send a letter*
J. Model Follow-up Letter Re-Stating Child's HLA Results for Parents, of Babies with First Degree Relatives with Type 1 Diabetes, Considering Participation in TEDDY
K. Site Specific Follow-up Letters Re-Stating Child's HLA Results for Parents, of Babies with First Degree Relatives with Type 1 Diabetes, Considering Participation in TEDDY
    1. Colorado
    2. Germany
    3. Georgia/Florida
    4. Washington
    5. *Sweden informs over the phone; does not send a letter*
    6. *Finland gave a brochure to everyone at hospital and informs over the phone; does not send a letter*
L. Model Follow-up Letter Re-Stating Child's HLA Results for General Population Parents Who Do Not Want to Participate in TEDDY – US Sites
M. Site Specific Follow-up Letter Re-Stating Child's HLA Results for General Population Parents Who Do Not Want to Participate in TEDDY
    1. Washington
    2. *Sweden informs over the phone; does not send a letter*

3. *Finland gave a brochure to everyone at hospital and informs over the phone; does not send a letter*

N. Model Follow-up Letter Re-Stating Child's HLA Results for Parents, of Babies with First Degree Relatives with Type 1 Diabetes, Who Do Not Want to Participate in TEDDY – US Sites

O. Site Specific Follow-up Letter Re-Stating Child's HLA Results for Parents, of Babies with First Degree Relatives with Type 1 Diabetes, Who Do Not Want to Participate in TEDDY
   1. Washington
   2. *Sweden informs over the phone; does not send a letter*
   3. *Finland gave a brochure to everyone at hospital and informs over the phone; does not send a letter*

P. Site Specific Letters Informing Parents of the High Risk HLA Results When Personal Contact Has Not Been Made
   1. Colorado

Q. Site Specific Explanation of Genetic Risk for Developing T1D Visual Aids
   1. Colorado
   2. Finland
   3. Georgia/Florida
   4. Germany
   5. Sweden
   6. *Washington does not use a visual aid*

R. General Information About Diabetes - Model

S. Frequently Asked Questions - Recruitment

A. MODEL LOW RISK LETTER:

Baby's Name
Address
Address
ID

Dear (person who completed screening informed consent);

When your baby, BABY'S NAME, was born on DATE, you agreed to take part in the TEDDY Study on type 1 (childhood) diabetes. We tested your baby's blood to see if the baby had the high-risk gene for type 1 diabetes. We now have your child's genetic test results. Your child does NOT have the high-risk gene for type 1 diabetes. This means that your child's risk of getting type 1 diabetes is not more than that of the average child. Based on your child's genetic test results, we cannot promise your child will never get type 1 diabetes. However, your child's risk is no more than that of the average child.

Thank you for your participation in this important study. No further testing is necessary for your child. We do ask that you contact us if your child ever gets type 1 diabetes in the future. Knowing this would help our study a lot. If you have any questions about this result or the TEDDY study, please call us (provide toll free number).

Again, thanks for helping us understand the causes of type 1diabetes in children.

Sincerely,
TEDDY INVESTIGATOR

B1. SITE SPECIFIC LOW RISK LETTER: COLORADO - GENERAL POPULATION

Barbara Davis Center for Childhood Diabetes
The University of Colorado at Denver and Health Sciences Center
4200 East 9th Avenue, C-245
Denver, Colorado 80262

Parent's Name
Address
Address
ID

Dear Parent (or person who completed screening informed consent),

On [SCREENING DATE], you agreed to take part in the screening phase of the TEDDY Study with the Barbara Davis Center for Childhood Diabetes at the University of Colorado. Your baby's blood was tested for the higher risk genes for type 1 diabetes.

Your child does NOT have the higher risk genes for type 1 diabetes. Based on these results, we cannot promise your child will never get the disease. Your child's risk is the same as the average child, which is 1 in 300. If your child ever develops diabetes in the future, please contact us - knowing this would help our study.

Thank you very much for taking part in this phase of the study. No more testing is needed for your child with TEDDY. Please call **303-315-0115** if you have any questions about the results or the TEDDY Study.

Thank you for helping us to learn about the causes of type 1 diabetes in children.

Sincerely,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

B1. SITE SPECIFIC LOW RISK LETTER:COLORADO – FIRST DEGREE RELATIVE

Barbara Davis Center for Childhood Diabetes
The University of Colorado at Denver and Health Sciences Center
4200 East 9th Avenue, C-245
Denver, Colorado 80262

Parent's Name
Address
Address
ID

Dear Parent (or person who completed screening informed consent),

On [SCREENING DATE], you agreed to take part in the screening phase of the TEDDY Study with the Barbara Davis Center for Childhood Diabetes at the University of Colorado. Your baby's blood was tested for the higher risk genes for type 1 diabetes.

Your child does NOT have the higher risk genes for type 1 diabetes. Based on these results, we cannot promise your child will never develop the disease. Because your child has a parent or sibling who has type 1 diabetes, they are still at some increased risk compared to a child with no diabetes in the family.

We recommend your child have testing for diabetes in the future. They can be tested through TrialNet, which is a nation-wide study. You may contact TrialNet when your child is 1 year old by calling 1-800-HALT-DM1 (1-800-425-8361). If your child ever develops diabetes in the future, please contact us - knowing this would help our study.

Thank you very much for taking part in the TEDDY Study. No more testing is needed for your child with TEDDY. If you have any questions about the results or the TEDDY Study, please call **303-315-0115**.

Thank you for helping us to learn about the causes of type 1 diabetes in children.

Sincerely,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

B2. SITE SPECIFIC LOW RISK LETTER: GERMANY – GENERAL POPULATION

INSTITUT FÜR DIABETESFORSCHUNG

Prof. Dr. med. A.-G. Ziegler
Leiterin der Klin. exp. Abteilung am Institut für Diabetesforschung
Kölner Platz 1, D-80804 München, Telefon 089 – 30 79 31 21, Telefax 089 – 30 81 733
Email: Teddy.Germany@lrz.uni-muenchen.de

Familie X
X-Str.

XX

München, 26. January 2024

Ergebnismitteilung über das Typ 1 Diabetes Risiko-Screening

Sehr geehrte Familie X,

bei Ihrem Kind X haben wir im Rahmen unserer TEDDY Studie eine genetische Typisierung durchgeführt, um das Typ 1 Diabetes Risiko zu bestimmen.

Die Untersuchung hat gezeigt, dass Ihr Kind **nicht** zu der Gruppe von Risikokindern zu rechnen ist. Das Risiko Ihres Kindes entspricht damit dem Durchschnittsrisiko der normalen Bevölkerung: etwa 3 von 1000 Kindern erkranken durchschnittlich an Typ 1 Diabetes. Wegen dieses geringen Risikos ist eine regelmäßige Kontrolle und Nachuntersuchung nicht notwendig.

Falls Ihr Kind dennoch im Laufe seines Lebens irgendwann an Typ 1 Diabetes erkranken sollte, möchten wir Sie herzlich bitten, uns dieses mitzuteilen.

Falls Sie zu diesem Testergebnis Fragen haben, rufen Sie uns bitte jederzeit kostenfrei an unter:

0800 – 3 38 33 39 bzw. 0800 – 33 – TEDDY

oder schreiben Sie uns an:

Teddy.Germany@lrz.uni-muenchen.de

Vielen Dank für Ihr Interesse und Ihre bisherige Teilnahme. Sie helfen dadurch mit, die Ursachen für Typ 1 Diabetes bei Kindern aufzudecken.

Mit freundlichen Grüßen,

Prof. Dr. med. A.-G. Ziegler A. Knopff

Bitte behandeln Sie diesen Befund im Interesse Ihres Kindes vertraulich.

B2. SITE SPECIFIC LOW RISK LETTER: GERMANY – FIRST DEGREE RELATIVE

INSTITUT FÜR DIABETESFORSCHUNG

Prof. Dr. med. A.-G. Ziegler
Leiterin der Klin. exp. Abteilung am Institut für Diabetesforschung
Kölner Platz 1, D-80804 München, Telefon 089 – 30 79 31 21, Telefax 089 – 30 81 733
Email: Teddy.Germany@lrz.uni-muenchen.de

Familie X
X-Str.

XX

München, 26. January 2024

Ergebnismitteilung über das Typ 1 Diabetes Risiko-Screening

Sehr geehrte Familie X,

bei Ihrem Kind X haben wir im Rahmen der TEDDY Studie eine genetische Typisierung durchgeführt, um das Typ 1 Diabetes Risiko zu bestimmen.

Die Untersuchung hat ergeben, dass Ihr Kind **nicht** zu der Gruppe von Risikokindern zu rechnen ist. Es besteht für Ihr Kind also kein erhöhtes genetisches Risiko einen Typ 1 Diabetes zu entwickeln. Damit steht allerdings nicht fest, dass Ihr Kind niemals an Diabetes erkranken wird. Es hat wie alle Kinder mit erkrankten Verwandten ein gewisses Risiko: ca. 4 von 100 dieser Kinder erkranken im Laufe ihres Lebens.

Falls Sie zu diesem Testergebnis Fragen haben, rufen Sie uns bitte jederzeit kostenfrei an unter:

0800 – 3 38 33 39 bzw. 0800 – 33 – TEDDY

oder schreiben Sie uns an:

Teddy.Germany@lrz.uni-muenchen.de

Wir empfehlen Ihnen, wenn Ihr Kind zwei Jahre alt ist, eine Antikörperbestimmung zur Diabetes-Früherkennung durchführen zu lassen. Bitte nehmen Sie kurz vorher Kontakt mit uns auf, damit wir Ihnen entsprechende Informationen zuschicken können.

Falls Ihr Kind einen Typ 1 Diabetes entwickeln sollte, möchten wir Sie bitten, uns das mitzuteilen, weil auch diese Information für unsere Studie wertvoll ist.

Mit herzlichem Dank für Ihre Mitarbeit,

Prof. Dr. med. A.-G. Ziegler A. Knopff

Bitte behandeln Sie diesen Befund im Interesse Ihres Kindes vertraulich.

B3. SITE SPECIFIC LOW RISK LETTER: GEORGIA/FLORIDA

Medical College of Georgia
GEORGIA'S HEALTH SCIENCES UNIVERSITY

Center for Biotechnology and Genomic Medicine

TEDDY
Center for Biotechnology and Genomic Medicine **Tel:** **1-888-225-7785**
Medical College of Georgia **Tel:** **706-721-4161**
1120 15th Street, CA-4124 **Fax:** **706-721-3688**
Augusta, GA 30912-2400 **Email:** **teddystudy@mcg.edu**

(date)
(parent address)
RE: (baby's name)

Dear (parent contact name):

Congratulations on the arrival of your new baby! You may recall that your baby participated in the TEDDY diabetes research study prior to leaving the hospital. Genetic testing was done to see if your baby has genes that would place him or her at risk for developing type 1 diabetes.

We are happy to report that we found no genes that place him or her at higher risk than the general public. This does not mean that your baby will never develop type 1 diabetes, but his or her chances are no higher than the average American, which is about 1 in 300. With the information we now have from your baby's gene testing and the family history you provided to us, we have determined that your baby does not qualify for further testing in the TEDDY study. If your child ever does develop diabetes or signs of diabetes, please contact us after you have seen to your child's immediate health needs with his or her primary medical care provider. Signs of diabetes include frequent urination and excessive thirst during the day and night, and unexplained weight loss.

If you have any questions about the TEDDY study or your baby's results, please give us a call locally at 721-4161, or for toll-free long distance dial 1-888-225-7785. The TEDDY office is open from 9am to 5pm, Monday through Friday. If we are not available, please leave us a message with your name, your child's name and your phone number. We will return your call as soon as possible.

Thank you for your participation in the TEDDY Study. It is because of the support for research from people like you that we are able to conduct this study and are making strides towards curing type 1 diabetes in your baby's lifetime.

Regards,

Diane Hopkins, MS, CCRC
TEDDY Study Manager

B4. SITE SPECIFIC LOW RISK LETTER: SWEDEN

TEDDY

Kära föräldrar!

Tack för ni varit med i TEDDY-studiens första del – screening- eller urvalsdelen.

Vi är mycket tacksamma för att vi i samband med förlossningen fick blod från mamma och ert nyfödda barns navelsträng. För fortsättningen av TEDDY-studien är er medverkan inte längre nödvändig.

Ert barns navelsträngsblod har undersökts för ärftlig risk för diabetes. Våra resultat visar att ert barn inte har högre ärftlig risk att utveckla typ 1 diabetes än de flesta barn i Sverige. Detta betyder inte att ert barn aldrig skulle kunna utveckla diabetes, men att barnets risk är liten.

Alla uppgifter, som skulle kunna identifiera er eller ert barn, har tagits bort ur vår databas. Blodproverna förvaras inlåsta i anslutning till våra forskningslaboratorier och endast några få personer har tillgång till de avidentifierade proverna.

Har ni några frågor kan ni kontakta vår samordnande forskningssköterska Gertie Hansson på telefon 040-332073 eller via e-mail: gertie.hansson@skane.se. Om ni vill ha närmare uppgifter om provresultat eller vill att proverna ska kastas måste ni ange det 6-siffriga nummer som finns angivet överst på adressetiketten.

På vår hemsida www.teddystudien.se kommer vi senare att presentera våra resultat allt eftersom de blir färdiga och kan publiceras.

Tack än en gång för att ni varit med i studien och bidragit till arbetet med att förhindra diabetes hos barn!

Åke Lernmark

Åke Lernmark, Professor i diabetesforskning
Universitetssjukhuset MAS, Lunds Universitet
Ansvarig för TEDDY-studien

B5. SITE SPECIFIC LOW RISK LETTER: WASHINGTON

PACIFIC NORTHWEST RESEARCH INSTITUTE

Parent of «Fname» «Lname»
«Address»
«City», «State» «Zip»

DATE

Dear Parent:

We would like to thank you for taking part in the TEDDY Study on type I (juvenile) diabetes. We have the test results for your child's sample that was taken while in the hospital shortly after birth.

«Fname»'s blood spot tested negative for the genetic markers of type 1 diabetes. This does not promise that «Fname» will never get diabetes. The good news is CHILD"S» risk is not more than that of the average child, who has a chance of about 1 in 300 or 0.3% of developing type 1 diabetes.

Thank you for your participation in this important study. No further testing is necessary for your child for this study. We do ask that you contact us if your child ever gets type 1 diabetes in the future. Knowing this would help our study a lot. If you have any questions regarding this result or any other question, please call us. Again, thanks for your participation in this research study to understand diabetes with the goal of prevention.

Sincerely Yours,

.

William A. Hagopian, MD, PhD,
Principal Investigator, Northwest TEDDY Study
Pacific NW Research Institute
206-860-6770
Toll Free: 1-888-324-2140

C. MODEL LETTER/POSTCARD FOR HIGHER RISK SUBJECTS TO NOTIFY THAT RESULTS ARE AVAILABLE

Dear (person who completed screening informed consent):

We would like to thank you for taking part in the TEDDY Study on type 1 (childhood) diabetes. We have your child's genetic test results. Please call (provide name, toll free number and hours to call) so we can discuss the test results with you. Thank you for your participation in this important study. We look forward to talking to you soon.

D. MODEL CALL TRACKING FORM

Child's Name: _____ Sex: _____
Child's DOB: _____

Mother's Name: _____ Father's Name: _____

Address: _____
_____
_____

Phone Number: _____

Alternate Phone Number: _____

Call Tracking:

Date_____ Time _____ Home Alt Message Comment:_____

Date_____ Time _____ Home Alt Message Comment:_____

Date_____ Time _____ Home Alt Message Comment:_____

Date_____ Time _____ Home Alt Message Comment:_____

Date_____ Time _____ Home Alt Message Comment:_____

Date_____ Time _____ Home Alt Message Comment:_____

Date_____ Time _____ Home Alt Message Comment:_____

Date_____ Time _____ Home Alt Message Comment:_____

E. MODEL SCRIPT FOR INITIAL TELEPHONE CONTACT TO EXPLAIN HIGH RISK HLA RESULTS TO GENERAL POPULATION FAMILIES – US SITES

"Hello, my name is _____ and I am calling from the TEDDY Study. May I speak with _____? Do you remember allowing us to test your baby for the high-risk gene for type 1 diabetes? Do you have a few minutes to talk?" [If yes continue. If no, record when to re-call and then say goodbye.]

Your baby's genetic test shows that your baby has the high-risk gene for type 1 diabetes. This means that your child has an increased risk for type 1 diabetes. This does not mean that your child will definitely get diabetes. Out of 100 babies with the same genetic test result as your baby, there would be approximately 3 babies who would develop diabetes. In the United States only 1 in 300 children get type 1 diabetes. So your baby is at higher risk for type 1 diabetes than the average child.

The TEDDY Study is interested in following children, like your baby, who are at increased risk for type 1 diabetes. We hope to find out what triggers diabetes in children with the high-risk gene. We hope you will agree to join the TEDDY study. We would like to keep track of your child's diet, colds, and viruses, stresses and allergies, and other life experiences. Participation in this study is completely voluntary. Can I send you some information about the study and call you in about a week?

Do you have any questions I can answer right now? If you have any questions about the study or your baby's test results before we call you again, feel free to call us at (toll free number). Thanks for helping us find the causes of type 1 diabetes. I will be calling you back in a week at (if possible set date and time for return call).

F. MODEL SCRIPT FOR INITIAL TELEPHONE CONTACT TO EXPLAIN HIGH RISK HLA RESULTS TO FAMILIES WITH FIRST DEGREE RELATIVES WITH TYPE 1 DIABETES – US SITES

"Hello, my name is _____ and I am calling from the TEDDY Study. May I speak with _____? Do you remember allowing us to test your baby for the high-risk gene for type 1 diabetes? Do you have a few minutes to talk?" [If yes continue. If no, record when to re-call and then say goodbye.]

Your baby's genetic test shows that your baby has the high-risk gene for type 1 diabetes. This means that your child has an increased risk for type 1 diabetes. This does not mean that your child will definitely get diabetes. Out of 100 babies with the same genetic test result as your baby, there would be approximately 14 babies who would develop diabetes. In the United States only 1 in 300 children get type 1 diabetes. So your baby is at higher risk for type 1 diabetes than the average child.

The TEDDY Study is interested in following children, like your baby, who are at increased risk for type 1 diabetes. We hope to find out what triggers diabetes in children with the high-risk gene. We hope you will agree to join the TEDDY study. We would like to keep track of your child's diet, colds, and viruses, stresses and allergies, and other life experiences. Participation in this study is completely voluntary. Can I send you some information about the study and call you in about a week?

Do you have any questions I can answer right now? If you have any questions about the study or your baby's test results before we call you again, feel free to call us at (toll free number). Thanks for helping us find the causes of type 1 diabetes. I will be calling you back in a week at (if possible set date and time for return call).

G. MODEL TELEPHONE MESSAGE SCRIPT

Hello, this is _____calling from the TEDDY Study. When your baby, BABY'S NAME, was born at HOSPITAL NAME you consented to have his/her cord blood screened. We have the results of that test and would like to speak with you at your earliest convenience. Please give me a call back at (xxx)xxx-xxxx. Thank you

H. MODEL FOLLOW-UP LETTER RE-STATING CHILD'S HLA RESULTS FOR GENERAL POPULATION PARENTS CONSIDERING PARTICIPATION IN TEDDY – US SITES

Dear (person contacted with HLA results)

Thank you for the opportunity to speak to you about your baby's genetic test results. As we discussed, your baby's genetic test shows that your baby has the high-risk gene for type 1 diabetes. This means that your child has an increased risk for type 1 diabetes. This does not mean that your child will definitely get diabetes. Out of 100 babies with the same genetic test result as your baby, there would be approximately 3 babies who would develop diabetes. In the United States only 1 in 300 children get type 1 diabetes. So your baby is at higher risk for type 1 diabetes than the average child.

The TEDDY Study is interested in following children, like your baby, who are at increased risk for type 1 diabetes. We hope to find out what triggers diabetes in children with the high-risk gene. We hope you will agree to join the TEDDY study. We would like to keep track of your child's diet, colds, and viruses, stresses and allergies, and other life experiences.

Participation in TEDDY is completely voluntary. Enclosed is some information about the TEDDY study. If you have any questions about the study or your baby's test results before we call you again, feel free to call us at (toll free number).

Thanks for helping us find the causes of type 1 diabetes. I will be calling you back in a week at (if possible set date and time for return call).

Sincerely
TEDDY Study staff

I1: SITE SPECIFIC FOLLOW-UP LETTER RE-STATING CHILD'S HLA RESULTS FOR GENERAL POPULATION PARENTS CONSIDERING PARTICIPATION IN TEDDY: COLORADO

Barbara Davis Center for Childhood Diabetes
The University of Colorado at Denver and Health Sciences Center
4200 East 9th Avenue, C-245
Denver, Colorado 80262

Parent's Name
Address
Address
ID

Dear Parents (or person signing the informed consent),

Thank you for taking the time to speak with us about [BABY NAME]'s genetic test results. On [SCREENING DATE], you agreed to take part in the screening phase of the TEDDY Study with the Barbara Davis Center for Childhood Diabetes at the University of Colorado. Your baby's blood was tested for the higher risk genes for type 1 diabetes.

As talked about on the phone, the test results show your child has the higher risk genes for type 1 diabetes. This does **not** mean your child will definitely get diabetes. The average risk of developing the disease is 1 in 300; your child's risk is 3 in 100. Not all children with the higher risk genes get diabetes. It is believed that other things must happen to "trigger", or cause a person to get the disease. The purpose of this study is to try to find out what the triggers are.

To learn what is important, the National Institutes of Health and six groups of research doctors around the world, including the Barbara Davis Center, are working together to follow children with the higher risk genes. We would like to keep track of your child's diet, illnesses, stressors, allergies and other life experiences, and test your child's blood to understand what triggers type 1 diabetes.

Enclosed is information to help you know more about the TEDDY Study. We look forward to talking with you again soon. Participating in this study is your choice. Because your child is at a higher risk for diabetes, we encourage you to think about joining TEDDY.

TEDDY staff will call you soon to talk about TEDDY in more detail. If you have any questions about the study or your baby's results before then, please call us at **303-315-0115**.

Thank you for helping us to learn about the causes of type 1 diabetes. We look forward to talking with you soon.

Sincerely,

Marian J. Rewers, MD, PhD

Principal Investigator, TEDDY Study

I2: SITE SPECIFIC FOLLOW-UP LETTER RE-STATING CHILD'S HLA RESULTS FOR GENERAL POPULATION PARENTS CONSIDERING PARTICIPATION IN TEDDY: GERMANY

INSTITUT FÜR DIABETESFORSCHUNG

Prof. Dr. med. A.-G. Ziegler
Leiterin der Klin. exp. Abteilung am Institut für Diabetesforschung
Kölner Platz 1, D-80804 München, Telefon 089 – 30 79 31 21, Telefax 089 – 30 81 733
Email: Teddy.Germany@lrz.uni-muenchen.de

Familie X
X-Str.

XX

München, 26. January 2024

Ergebnismitteilung über das Typ 1 Diabetes Risiko-Screening

Sehr geehrte Familie X,

bei Ihrem Kind X haben wir im Rahmen unserer TEDDY Studie eine genetische Typisierung durchgeführt, um das Typ 1 Diabetes Risiko zu bestimmen.

Wie bereits telefonisch besprochen, wurden dabei Risikogene für Typ 1 Diabetes festgestellt. Das bedeutet, dass Ihr Kind ein erhöhtes genetisches Risiko hat, an Typ 1 Diabetes zu erkranken. Das bedeutet aber nicht, dass Ihr Kind diese Krankheit auf jeden Fall entwickeln wird. Von 100 Kindern mit Risikogenen werden nur etwa 3 tatsächlich einen Typ 1 Diabetes bekommen. Bei Kindern ohne Risikogenen erkrankt im Vergleich etwa 3 von 1000 Kindern.

Die TEDDY Studie untersucht Kinder wie Ihres und hilft herauszufinden, wie Typ 1 Diabetes zu verhindern ist. Wir würden uns daher freuen, wenn Sie sich zur Teilnahme an der TEDDY Studie bereit erklären. Die Teilnahme ist völlig freiwillig.

Wir schicken Ihnen heute einige Informationen zur Studie mit und werden uns in etwa einer Woche wieder bei Ihnen melden. Falls Sie schon vorher Fragen zum Testergebnis oder zu TEDDY haben, rufen Sie uns bitte jederzeit kostenfrei an unter:

0800 – 3 38 33 39 bzw. 0800 – 33 – TEDDY

oder schreiben Sie uns an:

Teddy.Germany@lrz.uni-muenchen.de

Vielen Dank für Ihr Interesse an TEDDY und Ihre bisherige Teilnahme. Sie helfen dadurch, die Ursachen für Typ 1 Diabetes bei Kindern aufzudecken.

Mit freundlichen Grüßen,

Dipl. troph. Ch. Winkler Prof. Dr. med. A.-G. Ziegler Dr. med. P. Achenbach

Bitte behandeln Sie diesen Befund im Interesse Ihres Kindes vertraulich.

I3: SITE SPECIFIC FOLLOW-UP LETTER RE-STATING CHILD'S HLA RESULTS FOR GENERAL POPULATION PARENTS CONSIDERING PARTICIPATION IN TEDDY: GEORGIA/FLORIDA

Medical College of Georgia
GEORGIA'S HEALTH SCIENCES UNIVERSITY

Center for Biotechnology and Genomic Medicine

TEDDY
Center for Biotechnology and Genomic Medicine **Tel: 1-888-225-7785**
Medical College of Georgia **Tel: 706-721-4161**
1120 15th Street, CA-4124 **Fax: 706-721-3688**
Augusta, GA 30912-2400 **Email: teddystudy@mcg.edu**

Date
Parent Address
RE: (baby's name)

Dear contact name:

Thank you for speaking with us today on the telephone. As we discussed, when your baby was born, he or she was tested for the genes that would put him or her at risk for developing type 1 diabetes (also known as insulin dependent and/or childhood onset diabetes). Your baby was found to be at higher risk than the general public for type 1 diabetes, based on his or her genetic (inherited) information. The risk of developing diabetes is 1 in 300 for the average baby. With the information we have now from your baby's gene testing and the family history you provided to us in your first screening, we have placed your baby into the higher risk category, meaning he or she has a risk of 3 in 100. Please keep in mind that this does not mean that your baby has diabetes now, nor does it mean that he or she will definitely become diabetic in the future. There is still much we do not know about the inherited and environmental causes of type 1 diabetes. Our research is striving to understand this disease better, with the ultimate goals of finding both preventions and a cure.

We would like to encourage you to have your child followed in the second part of our research study. The TEDDY Study is interested in following children who are at increased risk for type 1 diabetes, like your baby. We hope to find out what triggers diabetes in children with high-risk genes. We would like to keep track of your child's diet, colds and viruses, stresses, allergies, and other life experiences. Although there is still no way to prevent diabetes from happening once it has begun, early detection can prevent serious illness and complications at the onset of diabetes. Our screenings are free of charge to you, and your participation in this research study is confidential.

I look forward to answering any questions you have regarding your participation in the TEDDY study, or about the TEDDY study or diabetes in general. Please do not hesitate to call us if we can help in any way.

Regards,

Diane I. Hopkins, MS, CCRC
TEDDY Study Manager

I4: SITE SPECIFIC FOLLOW-UP LETTER RE-STATING CHILD'S HLA RESULTS FOR GENERAL POPULATION PARENTS CONSIDERING PARTICIPATION IN TEDDY: WASHINGTON

PACIFIC NORTHWEST RESEARCH INSTITUTE

Parent of «Fname» «Lname»
«Address»
«City», «State» «Zip»

DATE

Dear <person contacted by phone with HLA results>,

Thank you for the opportunity to speak to you about your baby's genetic test results. As we discussed on the phone, your baby's genetic test shows that your baby has high-risk genes for type 1 diabetes. This means that your child has an increased risk for type 1 diabetes. This does not mean that your child will definitely get diabetes. Out of 100 babies with the same genetic test result as your baby, there would be approximately 3 babies who would develop diabetes.

The TEDDY Study is interested in following children who are at increased risk for type 1 diabetes. We hope to find out what triggers diabetes in children with high-risk genes. We hope you will agree to join the TEDDY study. We would like to keep track of your child's diet, colds, and viruses, stresses and allergies, and other life experiences.

Participation in TEDDY is completely voluntary. Enclosed is some information about the TEDDY Study including the consent form that you will need to sign to participate. If you have any questions about the study or your baby's test results before we call you again, feel free to call us at 1-888-324-2140.

Thanks for helping us find the causes of type 1 diabetes. I will be calling you back in a week at <date and time> to review these forms and answer any questions.

Sincerely,
<TEDDY Staff Member who reported results>

J. MODEL FOLLOW-UP LETTER RE-STATING CHILD'S HLA RESULTS FOR PARENTS, OF BABIES WITH FIRST DEGREE RELATIVES WITH TID, WHO ARE CONSIDERING PARTICIPATION IN TEDDY – US SITES

Dear (person contacted with HLA results)

Thank you for the opportunity to speak to you about your baby's genetic test results. As we discussed, your baby's genetic test shows that your baby has the high-risk gene for type 1 diabetes. This means that your child has an increased risk for type 1 diabetes. This does not mean that your child will definitely get diabetes. Out of 100 babies with the same genetic test result as your baby, there would be approximately 14 babies who would develop diabetes. In the United States, only 1 in 300 children get type 1 diabetes. So your baby is at higher risk for type 1 diabetes than the average child.

The TEDDY Study is interested in following children, like your baby, who are at increased risk for type 1 diabetes. We hope to find out what triggers diabetes in children with the high-risk gene. We hope you will agree to join the TEDDY study. We would like to keep track of your child's diet, colds, and viruses, stresses and allergies, and other life experiences.

Participation in TEDDY is completely voluntary. Enclosed is some information about the TEDDY study. If you have any questions about the study or your baby's test results before we call you again, feel free to call us at (toll free number).

Thanks for helping us find the causes of type 1 diabetes. I will be calling you back in a week at (if possible set date and time for return call).

Sincerely
TEDDY Study staff

K1. SITE-SPECIFIC FOLLOW-UP LETTER RE-STATING CHILD'S HLA RESULTS FOR PARENTS, OF BABIES WITH FIRST DEGREE RELATIVES WITH TID, WHO ARE CONSIDERING PARTICIPATION IN TEDDY: COLORADO

Barbara Davis Center for Childhood Diabetes
The University of Colorado at Denver and Health Sciences Center
4200 East 9th Avenue, C-245
Denver, Colorado 80262

Parent's Name
Address
Address
ID

Dear Parents (or person signing the informed consent),

Thank you for taking the time to speak with us on the phone about [BABY"S NAME]'s genetic test results. On [SCREENING DATE], you agreed to take part in the screening phase of the TEDDY Study with the Barbara Davis Center for Childhood Diabetes at the University of Colorado. You baby's blood was tested for the higher risk genes for type 1 diabetes.

As talked about on the phone, the test results show your baby has the higher risk genes for type 1 diabetes. This does **not** mean your baby will definitely get diabetes. The average risk of developing the disease is 1 in 300; your child's risk is 14 in 100. Not all children with the higher risk genes get diabetes. It is believed that other things must happen to "trigger", or cause a person to get the disease. The purpose of this study is to try to find out what the triggers are.

To learn what is important, the National Institutes of Health and six groups of research doctors around the world, including the Barbara Davis Center, are working together to follow children with the higher risk genes. We would like to keep track of your child's diet, illnesses, stressors, allergies and other life experiences, and test your child's blood to understand what triggers type 1 diabetes.

Enclosed is information to help you know more about the TEDDY Study. We look forward to talking with you again soon. Participating in this study is your choice. Because your child is at a higher risk for diabetes, we encourage you to think about joining TEDDY.

TEDDY staff will call you soon to talk about TEDDY in more detail. If you have any questions about the study or your baby's results before then, please call us at **303-315-0115**.

Thank you for helping us to learn about the causes of type 1 diabetes. We look forward to talking with you soon.

Sincerely,

Marian J. Rewers, MD, PhD

Principal Investigator, TEDDY Study

K2. SITE-SPECIFIC FOLLOW-UP LETTER RE-STATING CHILD'S HLA RESULTS FOR PARENTS, OF BABIES WITH FIRST DEGREE RELATIVES WITH TID, WHO ARE CONSIDERING PARTICIPATION IN TEDDY: GERMANY

INSTITUT FÜR DIABETESFORSCHUNG

Prof. Dr. med. A.-G. Ziegler
Leiterin der Klin. exp. Abteilung am Institut für Diabetesforschung
Kölner Platz 1, D-80804 München, Telefon 089 – 30 79 31 21, Telefax 089 – 30 81 733
Email: Teddy.Germany@lrz.uni-muenchen.de

Familie X
X-Straße

XX

München, 26. January 2024

Ergebnismitteilung über das Typ 1 Diabetes Risiko-Screening

Sehr geehrte Familie X,

bei Ihrem Kind X haben wir im Rahmen unserer TEDDY Studie eine genetische Typisierung durchgeführt, um das Typ 1 Diabetes Risiko zu bestimmen.

Wie bereits telefonisch mit Ihnen besprochen, haben wir bei der genetischen Typisierung Ihres Kindes Risikogene für Typ 1 Diabetes festgestellt. Das bedeutet, dass Ihr Kind ein erhöhtes genetisches Risiko hat, an Typ 1 Diabetes zu erkranken. Das bedeutet aber nicht, dass Ihr Kind diese Krankheit auf jeden Fall entwickeln wird. Von 100 Kindern mit Risikogenen werden etwa 14 tatsächlich einen Typ 1 Diabetes bekommen. Bei Kindern ohne Risikogenen, die einen erkrankten Verwandten haben, entwickeln im Vergleich etwa 4 von 100 einen Typ 1 Diabetes.

Unsere TEDDY Studie untersucht Kinder wie Ihres und hilft herauszufinden, wie Typ 1 Diabetes zu verhindern ist. Wir würden uns daher freuen, wenn Sie sich zur Teilnahme an unserer Studie bereit erklären. Die Teilnahme ist völlig freiwillig.

Wir schicken Ihnen heute einige Informationen zur Studie mit und werden uns in etwa einer Woche wieder bei Ihnen melden. Falls Sie vorher schon Fragen zum Testergebnis oder zu TEDDY haben, rufen Sie uns bitte jederzeit kostenfrei an unter:

0800 – 3 38 33 39 bzw. 0800 – 33 – TEDDY

oder schreiben Sie uns an:

Teddy.Germany@lrz.uni-muenchen.de

Vielen Dank für Ihr Interesse an TEDDY und Ihre bisherige Teilnahme. Sie helfen dadurch mit, die Ursachen für Typ 1 Diabetes bei Kindern aufzudecken.

Mit freundlichen Grüßen,

Dipl. troph. Ch. Winkler Prof. Dr. med. A.-G. Ziegler Dr. med. P. Achenbach

Bitte behandeln Sie diesen Befund im Interesse Ihres Kindes vertraulich.

K3. SITE-SPECIFIC FOLLOW-UP LETTER RE-STATING CHILD'S HLA RESULTS FOR PARENTS, OF BABIES WITH FIRST DEGREE RELATIVES WITH TID, WHO ARE CONSIDERING PARTICIPATION IN TEDDY: GEORGIA/FLORIDA

Medical College of Georgia
GEORGIA'S HEALTH SCIENCES UNIVERSITY

Center for Biotechnology and Genomic Medicine

TEDDY
Center for Biotechnology and Genomic Medicine **Tel:** **1-888-225-7785**
Medical College of Georgia **Tel:** **706-721-4161**
1120 15th Street, CA-4124 **Fax:** **706-721-3688**
Augusta, GA 30912-2400 **Email:** **teddystudy@mcg.edu**

Date
Parent Address
RE: (baby's name)

Dear contact name:

Thank you for speaking with us today on the telephone. As we discussed, when your baby was born, he or she was tested for the genes that would put him or her at risk for developing type 1 diabetes (also known as insulin dependent and/or childhood onset diabetes). Your baby was found to be at higher risk than the general public for type 1 diabetes, based on his or her genetic (inherited) information. The risk of developing diabetes is 1 in 300 for the average baby. With the information we have now from your baby's gene testing and the family history of type 1 diabetes you provided to us in your first screening, we have placed your baby into the higher risk category, meaning he or she has a risk of 14 in 100. Please keep in mind that this does not mean that your baby has diabetes now, nor does it mean that he or she will definitely become diabetic in the future. There is still much we do not know about the inherited and environmental causes of type 1 diabetes. Our research is striving to understand this disease better, with the ultimate goals of finding both preventions and a cure.

We would like to encourage you to have your child followed in the second part of our research study. The TEDDY Study is interested in following children who are at increased risk for type 1 diabetes, like your baby. We hope to find out what triggers diabetes in children with high-risk genes. We would like to keep track of your child's diet, colds and viruses, stresses, allergies, and other life experiences. Although there is still no way to prevent diabetes from happening once it has begun, early detection can prevent serious illness and complications at the onset of diabetes. Our screenings are free of charge to you, and your participation in this research study is confidential.

I look forward to answering any questions you have regarding your participation in the TEDDY study, or about the TEDDY study or diabetes in general. Please do not hesitate to call us if we can help in any way.

Regards,

Diane I. Hopkins, MS, CCRC
TEDDY Study Manager

K4. SITE-SPECIFIC FOLLOW-UP LETTER RE-STATING CHILD'S HLA RESULTS FOR PARENTS, OF BABIES WITH FIRST DEGREE RELATIVES WITH TID, WHO ARE CONSIDERING PARTICIPATION IN TEDDY: WASHINGTON

PACIFIC NORTHWEST RESEARCH INSTITUTE

Parent of «Fname» «Lname»
«Address»
«City», «State» «Zip»

DATE

Dear <person contacted by phone with HLA results>,

Thank you for the opportunity to speak to you about your baby's genetic test results. As we discussed on the phone, your baby's genetic test shows that your baby has high-risk genes for type 1 diabetes. This means that your child has an increased risk for type 1 diabetes. This does not mean that your child will definitely get diabetes. Out of 100 babies with the same genetic test result as your baby, there would be approximately 14 babies who would develop diabetes.

The TEDDY Study is interested in following children who are at increased risk for type 1 diabetes. We hope to find out what triggers diabetes in children with high-risk genes. We hope you will agree to join the TEDDY study. We would like to keep track of your child's diet, colds, and viruses, stresses and allergies, and other life experiences.

Participation in TEDDY is completely voluntary. Enclosed is some information about the TEDDY Study including the consent form that you will need to sign to participate. If you have any questions about the study or your baby's test results before we call you again, feel free to call us at 1-888-324-2140.

Thanks for helping us find the causes of type 1 diabetes. I will be calling you back in a week at <date and time> to review these forms and answer any questions.

Sincerely,
<TEDDY Staff Member who reported results>

L. MODEL FOLLOW-UP LETTER RE-STATING CHILD'S HLA RESULTS FOR GENERAL POPULATION PARENTS WHO DO NOT WANT TO PARTICIPATE IN TEDDY – US SITES

Dear (person contacted with HLA results)

Thank you for the opportunity to speak to you about your baby's genetic test results. As we discussed, your baby's genetic test shows that your baby has the high-risk gene for type 1 diabetes. This means that your child has an increased risk for type 1 diabetes. This does not mean that your child will definitely get diabetes. Out of 100 babies with the same genetic test result as your baby, there would be approximately 3 babies who would develop diabetes. In the United States, only 1 in 300 children get type 1 diabetes. So your baby is at higher risk for type 1 diabetes than the average child.

The TEDDY Study is interested in following children who are at increased risk for type 1 diabetes. We hope to find out what triggers diabetes in children with the high-risk gene.

We understand that you do not wish to participate in the TEDDY study. We do ask that you contact us if your child ever gets type 1 diabetes in the future. Knowing this would help our study a lot. If you have any questions about your baby's genetic test result or the TEDDY study, please call us at any time (provide toll free number). Thank you for having your child screened for the diabetes high-risk gene. Best wishes to your family.

Sincerely,
TEDDY Study staff

M1. SITE SPECIFIC FOLLOW-UP LETTER RE-STATING CHILD'S HLA RESULTS FOR GENERAL POPULATION PARENTS WHO DO NOT WANT TO PARTICIPATE IN TEDDY: WASHINGTON

PNRI PACIFIC NORTHWEST RESEARCH INSTITUTE

Parent of «Fname» «Lname»
«Address»
«City», «State» «Zip»

DATE

Dear <person contacted by phone with HLA results>,

Thank you for the opportunity to speak to you about your baby's genetic test results. As we discussed on the phone, your baby's genetic test shows that your baby has high-risk genes for type 1 diabetes. This means that your child has an increased risk for type 1 diabetes. This does not mean that your child will definitely get diabetes. Out of 100 babies with the same genetic test result as your baby, there would be approximately 3 babies who would develop diabetes.

The TEDDY Study is interested in following children who are at increased risk for type 1 diabetes. We hope to find out what triggers diabetes in children with high-risk genes.

We understand that you do not wish to participate in the TEDDY Study at this time. We do ask that you contact us if your child ever gets type 1 diabetes in the future. Knowing this would help our study a lot. If you have any questions about your baby's genetic test result or the TEDDY Study, please call us at any time at 1-888-324-2140. Thank you for having your child screened for diabetes high-risk genes. Best wishes to your family.

Sincerely,
<TEDDY Staff Member who reported results>

N. MODEL FOLLOW-UP LETTER RE-STATING CHILD'S HLA RESULTS FOR PARENTS, OF BABIES WITH FIRST DEGREE RELATIVES WITH TID, WHO DO NOT WANT TO PARTICIPATE IN TEDDY – US SITES

Dear (person contacted with HLA results)

Thank you for the opportunity to speak to you about your baby's genetic test results. As we discussed, your baby's genetic test shows that your baby has the high-risk gene for type 1 diabetes. This means that your child has an increased risk for type 1 diabetes. This does not mean that your child will definitely get diabetes. Out of 100 babies with the same genetic test result as your baby, there would be approximately 14 babies who would develop diabetes. In the United States, only 1 in 300 children get type 1 diabetes. So your baby is at higher risk for type 1 diabetes than the average child.

The TEDDY Study is interested in following children who are at increased risk for type 1 diabetes. We hope to find out what triggers diabetes in children with the high-risk gene.

We understand that you do not wish to participate in the TEDDY study. We do ask that you contact us if your child ever gets type 1 diabetes in the future. Knowing this would help our study a lot. If you have any questions about your baby's genetic test result or the TEDDY study, please call us at any time (provide toll free number). Thank you for having your child screened for the diabetes high-risk gene. Best wishes to your family.

Sincerely,
TEDDY Study staff

O1. SITE SPECIFIC FOLLOW-UP LETTER RE-STATING CHILD'S HLA RESULTS FOR PARENTS, OF BABIES WITH FIRST DEGREE RELATIVES WITH TID, WHO DO NOT WANT TO PARTICIPATE IN TEDDY: WASHINGTON

PACIFIC NORTHWEST RESEARCH INSTITUTE

Parent of «Fname» «Lname»
«Address»
«City», «State» «Zip»

DATE

Dear <person contacted by phone with HLA results>,

Thank you for the opportunity to speak to you about your baby's genetic test results. As we discussed on the phone, your baby's genetic test shows that your baby has high-risk genes for type 1 diabetes. This means that your child has an increased risk for type 1 diabetes. This does not mean that your child will definitely get diabetes. Out of 100 babies with the same genetic test result as your baby, there would be approximately 14 babies who would develop diabetes.

The TEDDY Study is interested in following children who are at increased risk for type 1 diabetes. We hope to find out what triggers diabetes in children with high-risk genes.

We understand that you do not wish to participate in the TEDDY Study at this time. We do ask that you contact us if your child ever gets type 1 diabetes in the future. Knowing this would help our study a lot. If you have any questions about your baby's genetic test result or the TEDDY Study, please call us at any time at 1-888-324-2140. Thank you for having your child screened for diabetes high-risk genes. Best wishes to your family.

Sincerely,
<TEDDY Staff Member who reported results>

P1. SITE SPECIFIC LETTERS INFORMING PARENTS OF THE HIGH RISK HLA RESULTS WHEN PERSONAL CONTACT HAS NOT BEEN MADE: COLORADO – GENERAL POPULATION

Barbara Davis Center for Childhood Diabetes
The University of Colorado at Denver and Health Sciences Center
4200 East 9th Avenue, C-245
Denver, Colorado 80262

Parent's Name
Address
Address
ID

Dear Parents (or person who signed the informed consent),

On [SCREENING DATE, you agreed to take part in the screening phase of the TEDDY Study with the Barbara Davis Center for Childhood Diabetes at the University of Colorado. Your baby's blood was tested for the higher risk genes for type 1 diabetes.

We have tried many times to contact you about your baby's results, but have not been able to reach you. The test results show your baby has the higher risk genes for type 1 diabetes. This does **not** mean your baby will definitely develop diabetes. The average risk of developing the disease is 1 in 300; your child's risk is 3 in 100. Not all children who have the higher risk genes get diabetes. It is believed that other things must happen to "trigger", or cause a person to get the disease. The purpose of this study is to try to find out what the triggers are.

To learn what is important, the National Institutes of Health and six groups of research doctors around the world, including the Barbara Davis Center, are working together to follow children with the higher risk genes. We would like to keep track of your child's diet, illnesses, stressors, allergies and other life experiences, and test your child's blood to understand what triggers type 1 diabetes.

Because your baby is at a higher risk, we encourage you to think about joining the TEDDY study. Please call us at **303-315-0115** if you have questions about the test results or would like to learn more about the TEDDY Study**.** To join TEDDY, you must call us ***before your baby is 4 months old***.

Thank you for helping us to learn about the causes of type 1 diabetes in children.

Sincerely,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

The Environmental Determinants of Diabetes in the Young
Phone: 303-315-0115 email: Teddy.Study@uchsc.edu Fax: 303-315-5987

P1. SITE SPECIFIC LETTERS INFORMING PARENTS OF THE HIGH RISK HLA RESULTS WHEN PERSONAL CONTACT HAS NOT BEEN MADE: COLORADO – FDR

Barbara Davis Center for Childhood Diabetes
The University of Colorado at Denver and Health Sciences Center
4200 East 9th Avenue, C-245
Denver, Colorado 80262

Parent's Name
Address
Address
ID

Dear Parents (or person who signed the informed consent),

On [SCREENING DATE], you agreed to take part in the screening phase of the TEDDY Study with the Barbara Davis Center for Childhood Diabetes at the University of Colorado. Your baby's blood was tested for the higher risk genes for type 1 diabetes.

We have tried many times to contact you about your baby's results, but have not been able to reach you. The test results show your baby has the higher risk genes for type 1 diabetes. This does **not** mean your baby will definitely develop diabetes. The average risk of developing the disease is 1 in 300; your child's risk is 14 in 100. Not all children who have the higher risk genes get diabetes. It is believed that other things must happen to "trigger", or cause a person to get the disease. The purpose of this study is to try to find out what the triggers are.

To learn what is important, the National Institutes of Health and six groups of research doctors around the world, including the Barbara Davis Center, are working together to follow children with the higher risk genes. We would like to keep track of your child's diet, illnesses, stressors, allergies and other life experiences, and test your child's blood to understand what triggers type 1 diabetes.

Because your baby is at a higher risk, we encourage you to think about joining the TEDDY study. Please call us at **303-315-0115** if you have questions about the test results or would like to learn more about the TEDDY Study**.** To join TEDDY, you must call us ***before your baby is 4 months old***.

Thank you for helping us to learn about the causes of type 1 diabetes in children.

Sincerely,

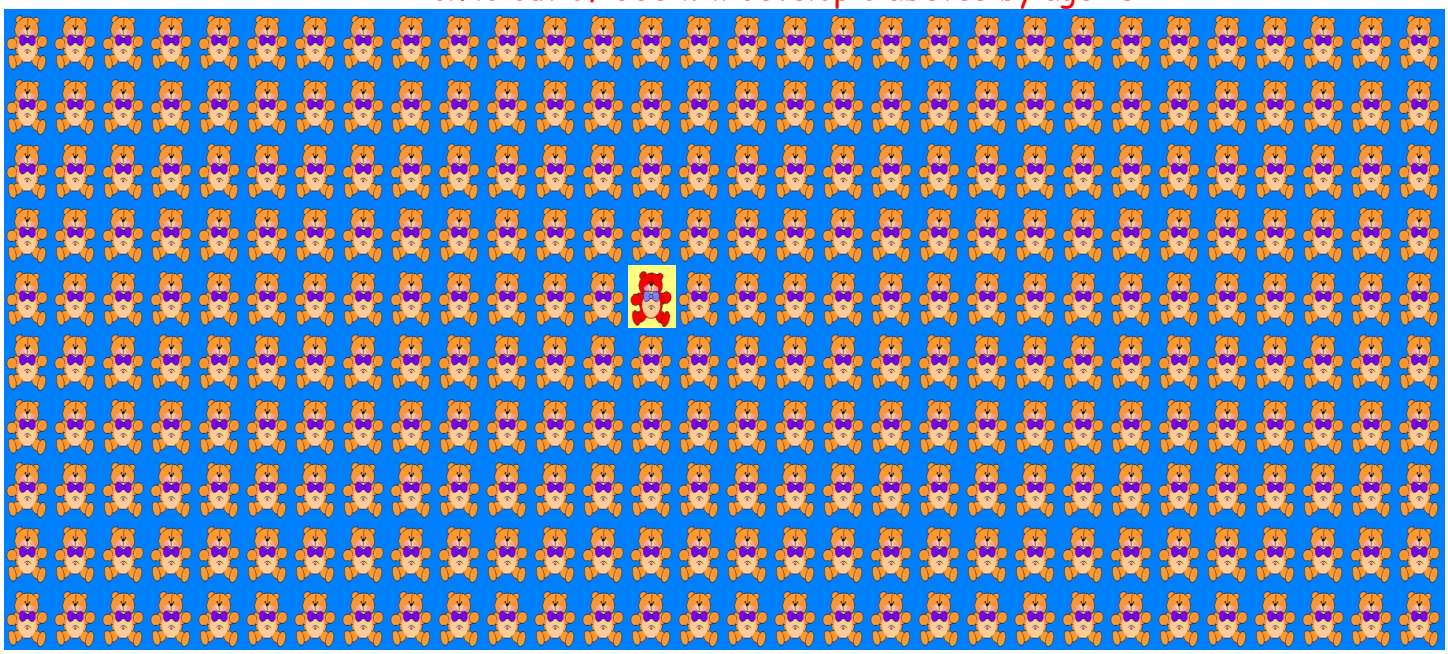
Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

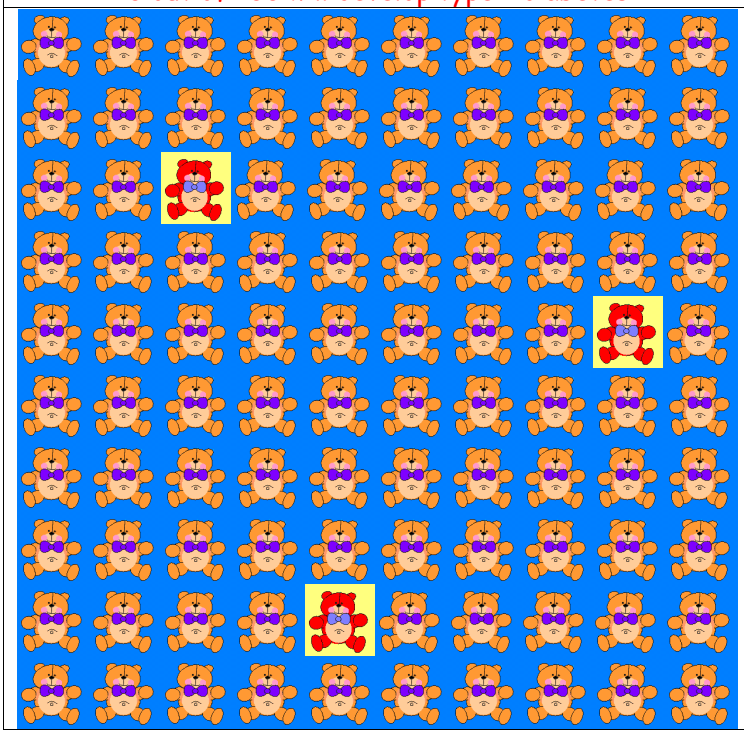
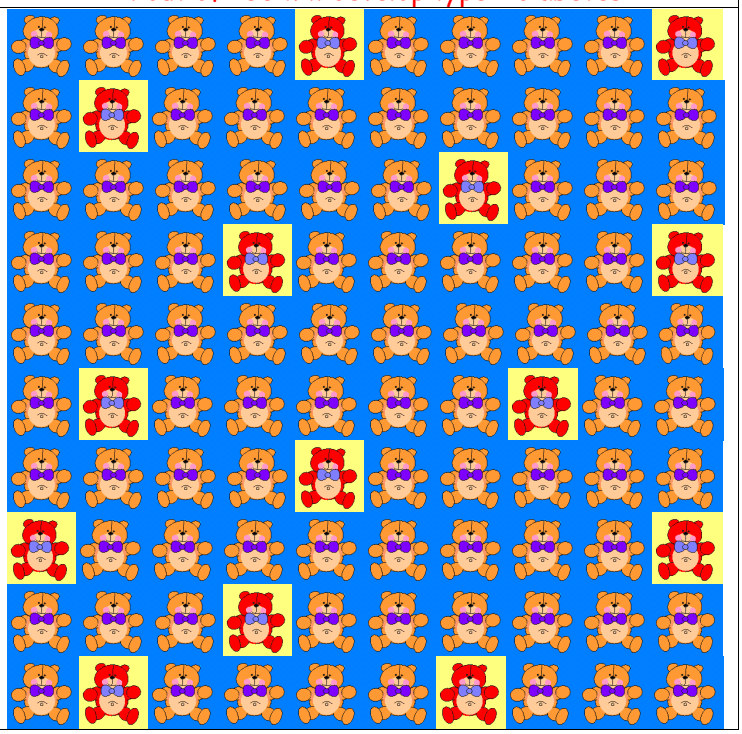
Q1. SITE SPECIFIC EXPLANATION OF GENETIC RISK FOR DEVELOPING T1D
VISUAL AIDS: COLORADO

THE GENETIC RISK OF DEVELOPING TYPE I DIABETES

In Colorado

1 child out of 300 will develop diabetes by age 15



Children with no diabetic relatives found by TEDDY at birth to have higher risk genes 3 out of 100 will develop type 1 diabetes	Children who have a diabetic parent or sibling and found by TEDDY at birth to have higher risk genes 14 out of 100 will develop type 1 diabetes
	

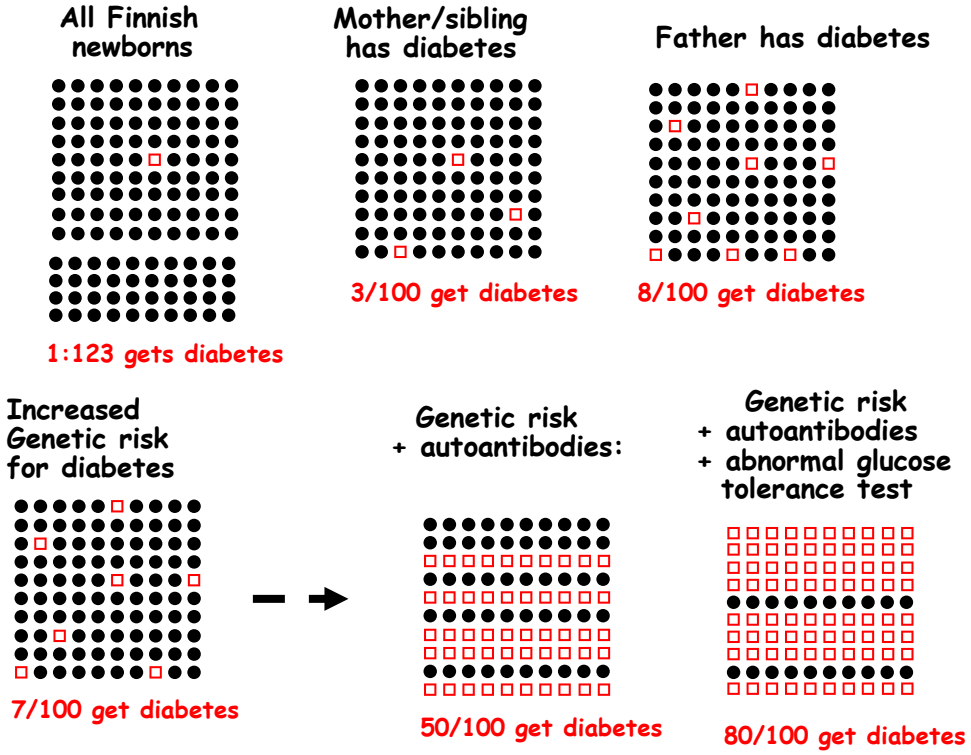
Q2. SITE SPECIFIC EXPLANATION OF GENETIC RISK FOR DEVELOPING T1D VISUAL AIDS: FINLAND

Estimating the risk for developing diabetes:

- *One out 123 Finnish newborns will develop diabetes before 15 years of age*
- *If the mother or sibling of the child has diabetes, approximately 3 children out of 100 will get diabetes.*
- *If the father of the child has diabetes, approximately 8 children out of 100 will get diabetes.*
- *If the child has a genetic susceptibility to develop diabetes (found by the genetic screening): 3-7 children out of 100 will develop diabetes*

---------- *If two or more species of diabetes associated autoantibodies have been found in the blood of a genetically susceptible child: over 50 children out of 100 will develop diabetes*

---------- *If, in addition, a reduced capacity to produce insulin has been found in an intravenous glucose tolerance test, over 80 children out of 100 will develop diabetes.*

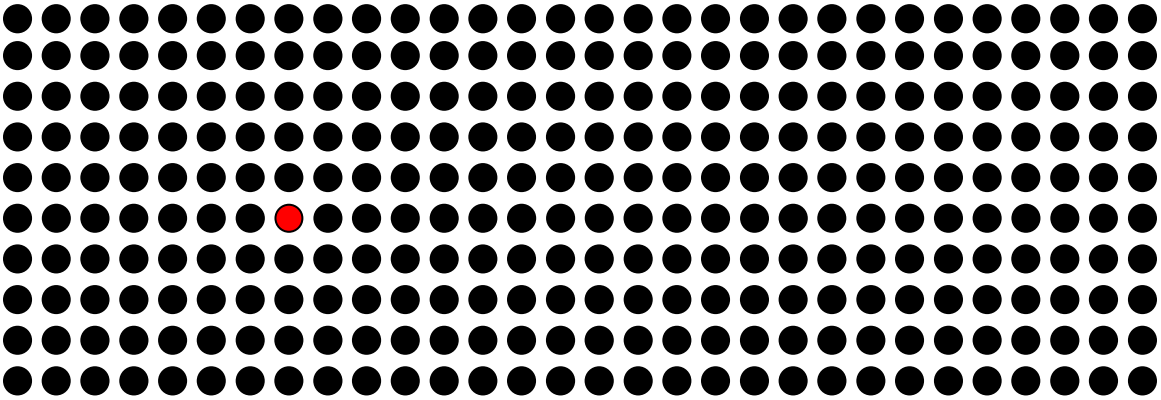


Q3. SITE SPECIFIC EXPLANATION OF GENETIC RISK FOR DEVELOPING T1D VISUAL AIDS: GEORGIA/FLORIDA

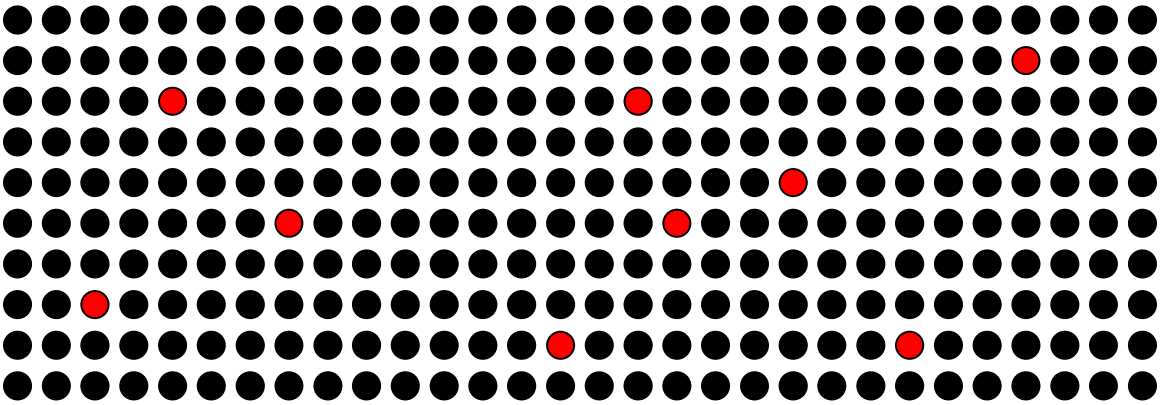
Georgia/Florida – Explanation of Genetic Risk Visual Aid, General Population:

What does my Baby's Risk Look Like?

The average baby born in the United States
has a risk of 1 in 300, or about a 0.3% chance
of developing type 1 diabetes. This means, for every 300 babies born, 1
will go on to develop type 1 diabetes.
1 in 300 looks like this:



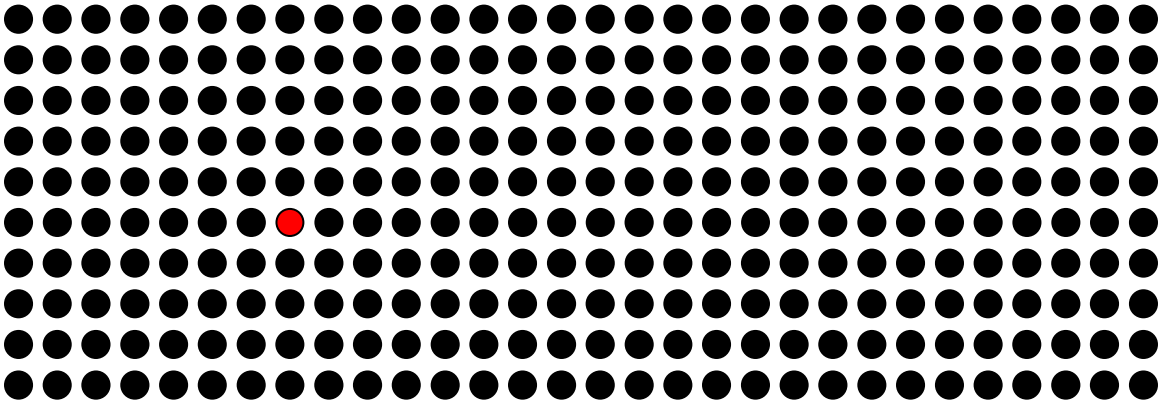
Your baby has genes that place him/her into the higher risk category,
which means he/she has a risk of 3 in 100, or about a 3% chance
of developing type 1 diabetes.
This is 10 times higher than the risk to babies who do not have these genes.
For every 100 babies who have the same genes as your baby,
3 will go on to develop type 1 diabetes.
3% (the same as 3 in 100 or 9 in 300) looks like this:



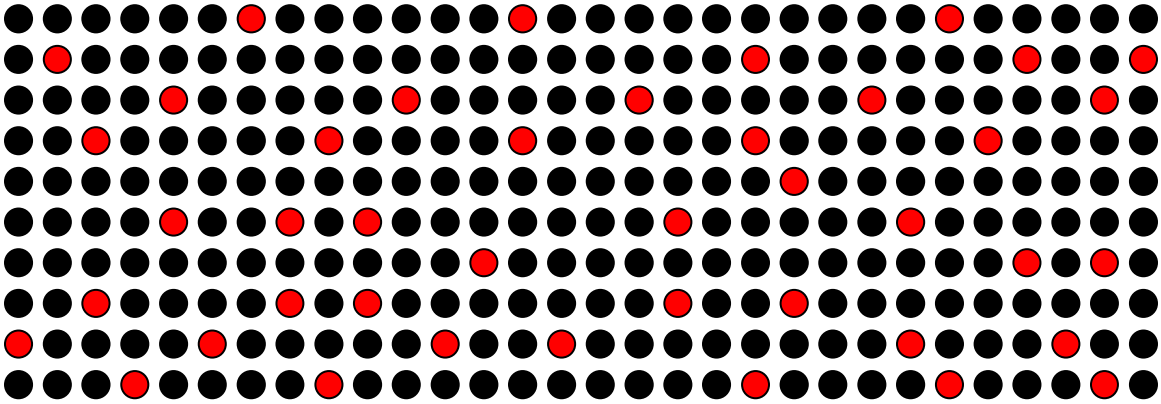
Georgia/Florida – Explanation of Genetic Risk Visual Aid, First Degree Relative:

What does my Baby's Risk Look Like?

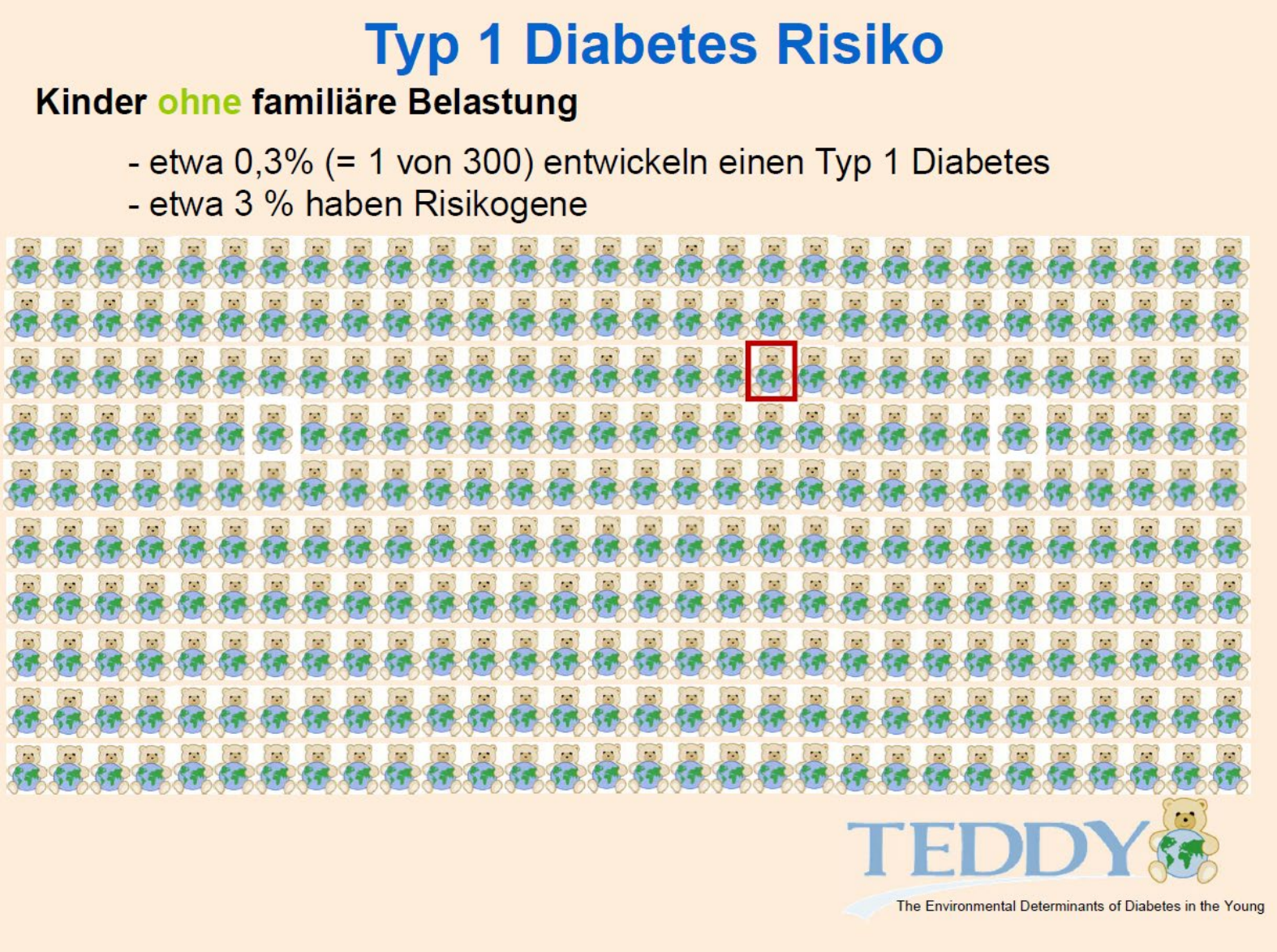
The average baby born in the United States
has a risk of 1 in 300, or about a 0.3% chance
of developing type 1 diabetes. This means, for every 300 babies born, 1
will go on to develop type 1 diabetes.
1 in 300 looks like this:

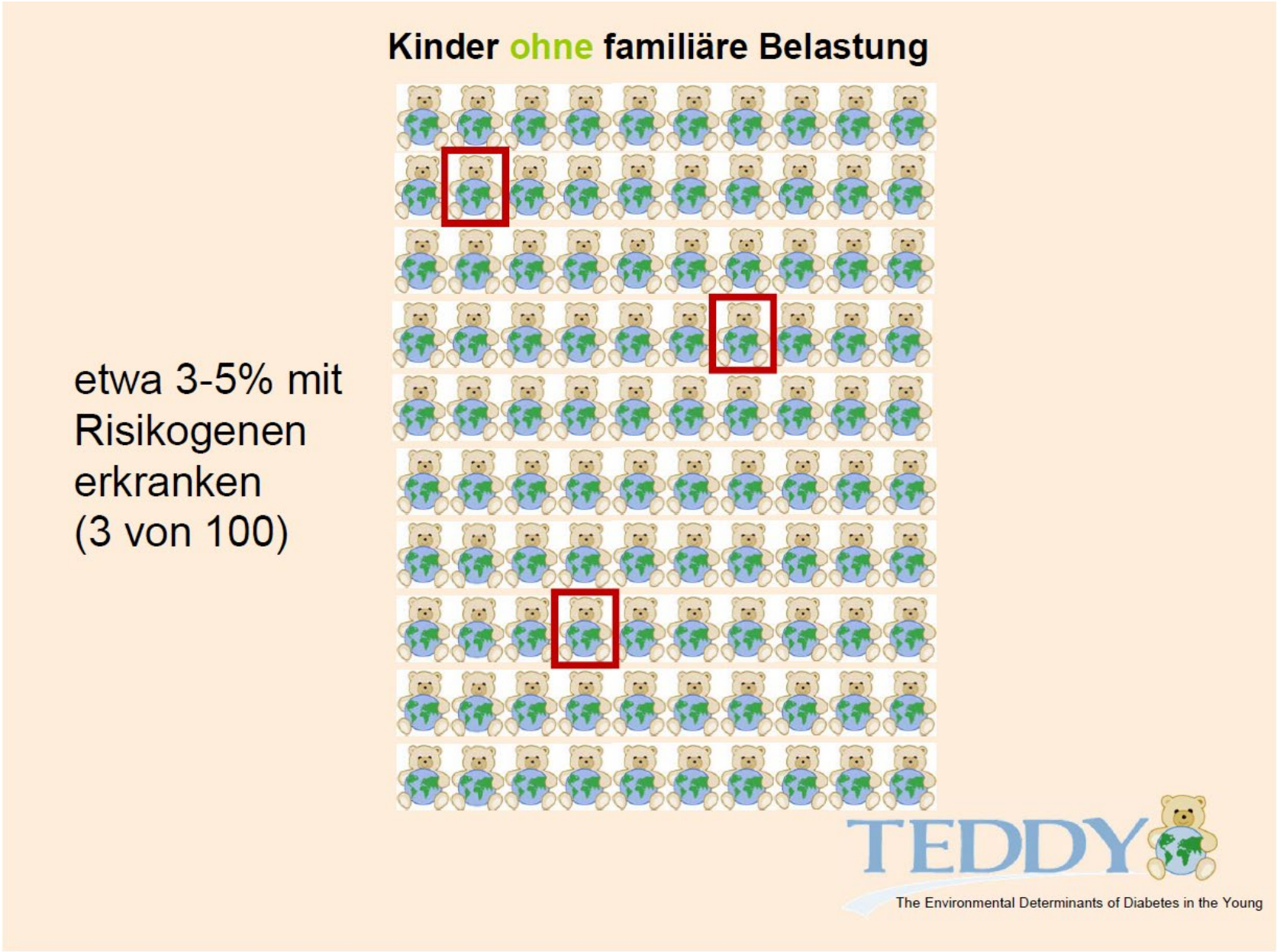


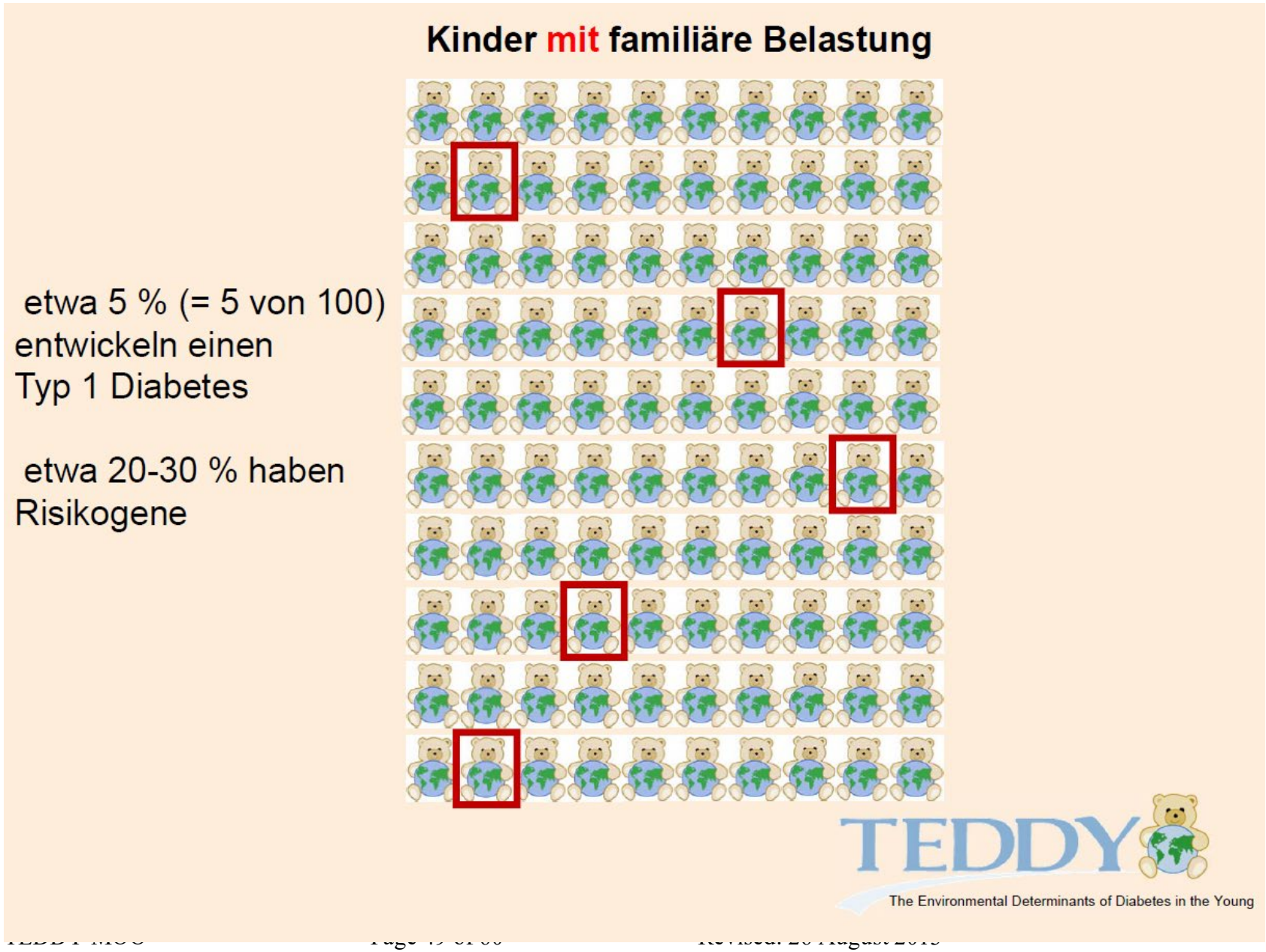
Your baby has genes and a family history of type 1 diabetes
that place him/her into the higher risk category,
which means he/she has a risk of 14 in 100, or about a 14% chance
of developing type 1 diabetes.
For every 100 babies who have the same genes as your baby,
14 will go on to develop type 1 diabetes.
14 in 100 (the same as 42 in 300) looks like this:

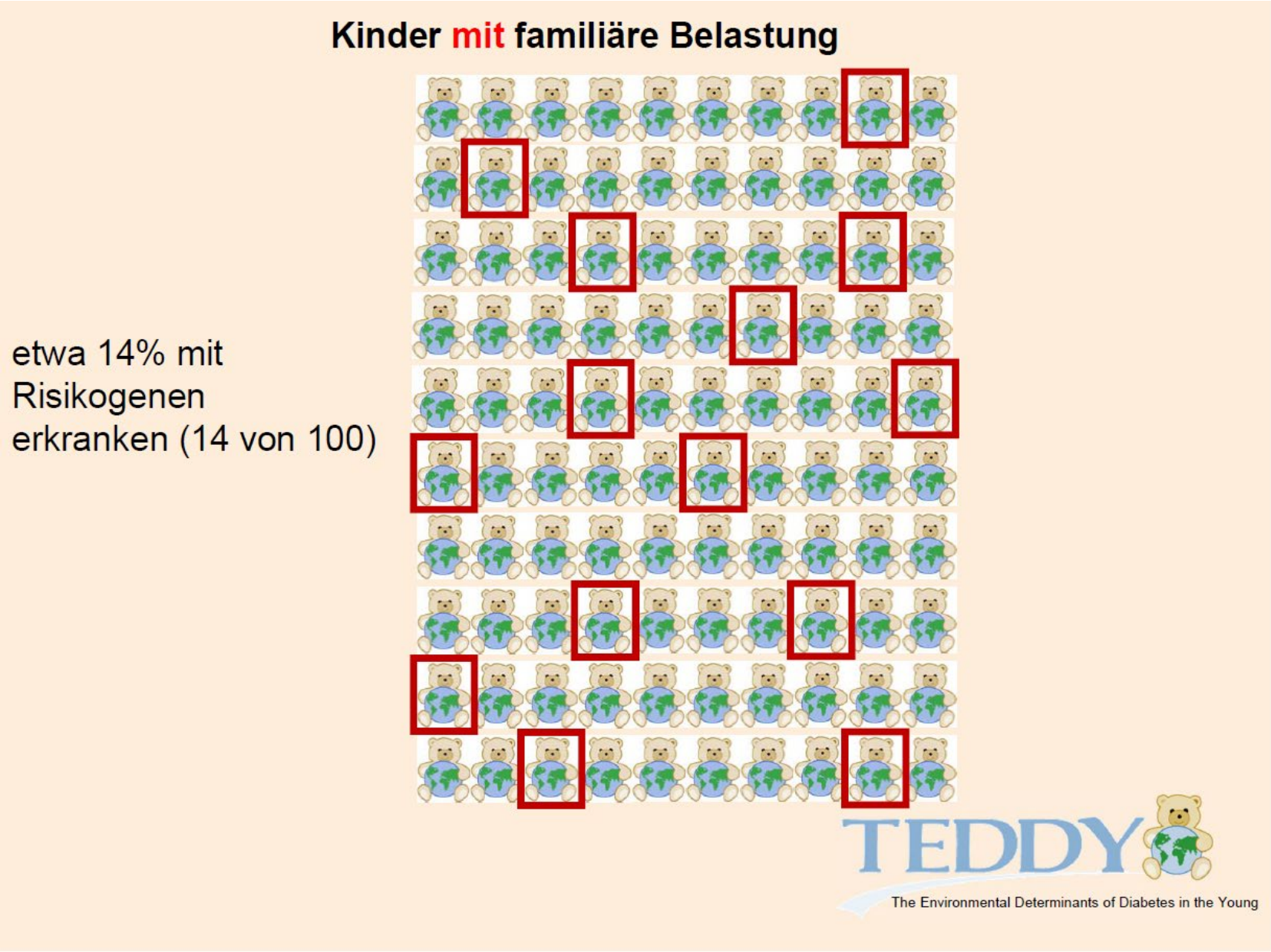


Q5. SITE SPECIFIC EXPLANATION OF GENETIC RISK FOR DEVELOPING T1D VISUAL AIDS: GERMANY

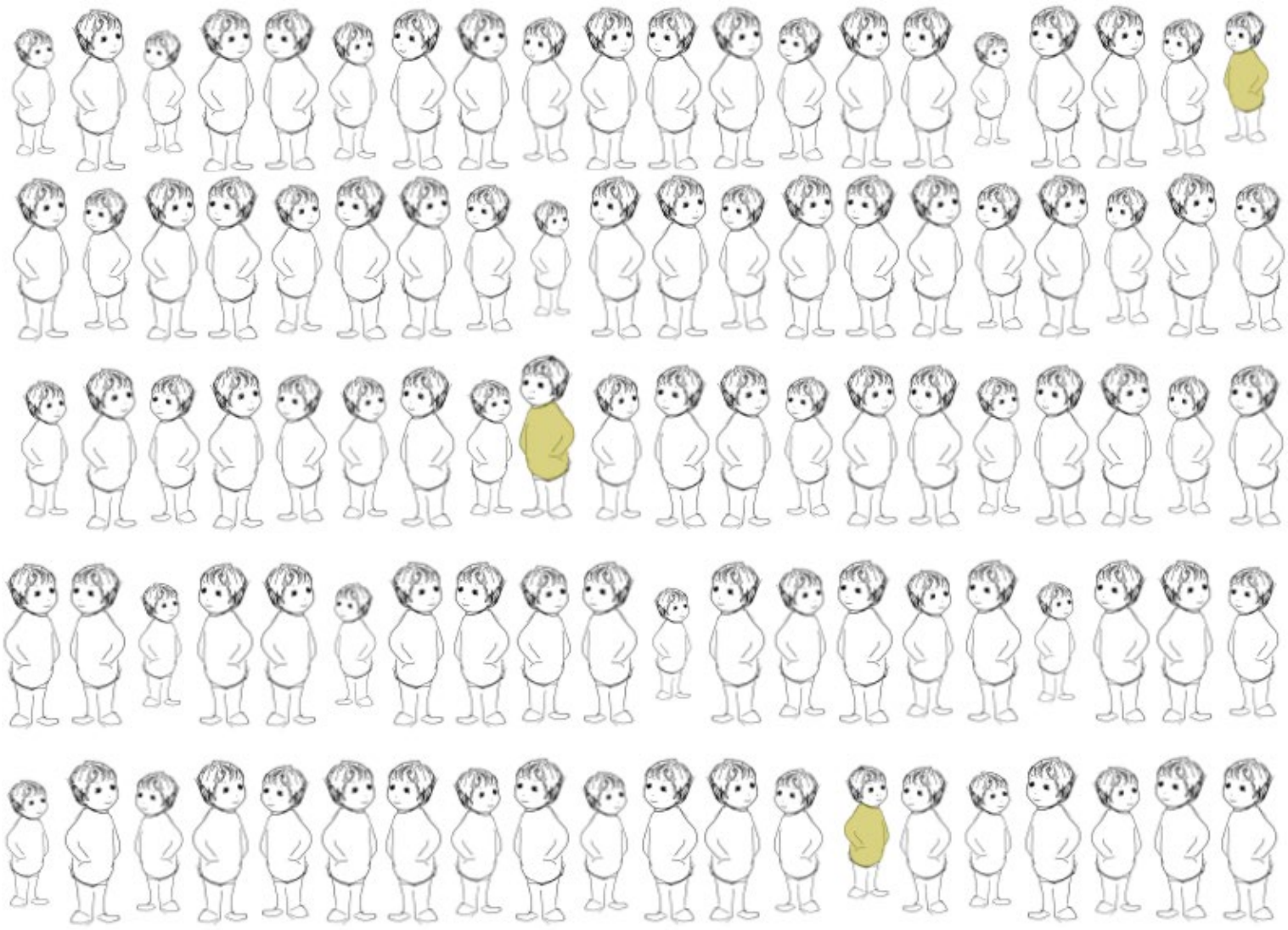



Kinder ohne familiäre Belastung
etwa 3-5% mit Risikogenen erkranken (3 von 100)
TEDDY
The Environmental Determinants of Diabetes in the Young


Kinder mit familiäre Belastung
etwa 5 % (= 5 von 100) entwickeln einen Typ 1 Diabetes
etwa 20-30 % haben Risikogene
TEDDY
The Environmental Determinants of Diabetes in the Young


Kinder mit familiäre Belastung
etwa 14% mit Risikogenen erkranken (14 von 100)
TEDDY
The Environmental Determinants of Diabetes in the Young

Q5. Site Specific Explanation of Genetic Risk for Developing T1D Visual Aids: SWEDEN



R. GENERAL INFORMATION ABOUT DIABETES - MODEL

Normally when you eat foods your body breaks them down into a type of sugar called glucose. Glucose is the main thing that our bodies use for energy. This sugar circulates into the blood where it is taken up into the cells for energy. Without this sugar our cells would not have the energy to function-it is very important. The way that the sugar gets out of the blood and into the cells is with insulin. Insulin is a hormone that is made by special cells called islet cells that are located in the pancreas. You can think of insulin as a key that unlocks a door.

There are 2 major kinds of diabetes, Type 1 and Type 2. Type 2 used to be called adult onset diabetes. It is the more common kind and is usually found in adults, although it is becoming more common in children. What happens with this kind of diabetes is that your body still makes insulin it just doesn't use it right or it becomes resistant to it. It's like the key doesn't fit the lock. When the cells become resistant to the insulin the sugar cannot get out of the blood and it can cause lots of problems. Because people with Type 2 diabetes still make insulin, they can sometimes control their diabetes by changing their diet, exercising more or taking oral medications.

Now BABY was screened for Type 1 diabetes, which is different and this is the type of diabetes that the TEDDY study is about. Type 1 diabetes used to be called juvenile diabetes because we thought only children could get it. Type 1 diabetes is an autoimmune disease. This means that the body's immune system, which should be fighting things that don't belong in the body (like a virus) gets confused and starts fighting the body's own cells. There are many different kinds of autoimmune diseases, but in the case of Type 1 diabetes the immune system starts fighting the islet cells in the pancreas that make insulin. This process can take a long time, many months to many years until eventually all of the islet cells are broken down and the body can't make insulin anymore. When the body can't make insulin then the sugar cannot get into the cells to be used for energy and it builds up in the blood. This is when diabetes occurs. Before a person actually gets Type 1 diabetes the autoimmune process is happening but no one knows, people feel fine and they look healthy. People can develop diabetes without being aware that something is going on, the sign or symptoms might be hard to recognize as diabetes. With this kind of diabetes, Type 1, people who get it eventually stop making insulin and so they must have insulin to survive. It is a disease that lasts forever and right now, unfortunately, there is no cure.

Part of what we know about Type 1 diabetes is that it is genetic. People with family members with Type 1 diabetes are more likely to get it and people who have certain genes are more likely to get it. But, not everyone with the genes or family member gets Type 1 diabetes so we believe that it is partially environmental- meaning there is probably something in the environment that may either trigger diabetes or else prevent it. Some environmental factors that may be involved are viruses, diet, stress or allergies. Our study is trying to find out what this trigger or prevention might be.

In the past, other studies that have looked at this, have studied kids that developed diabetes and then asked their parents about environmental exposures that happened in the past. This isn't the best way to do it; most children develop diabetes between the ages of 8 and 12, but we know from studying the progression of the disease that the autoimmune process can start when these

children are very young- it may take years for diabetes to actually occur. It is very hard for parents of kids that age to remember back when their children were babies to see what they might have been exposed to.

What we are doing here at TEDDY is trying to study diabetes **before** it occurs. We are hoping to gather information the same way on a big group of children that are all at risk for developing diabetes. This study includes children from around the world participating in this same study at 5 other sites. Most of the children in the study will never develop diabetes but some will. Eventually we expect to see patterns of differences between the children who develop diabetes and the ones that don't. The kinds of factors that we are looking at in this study have all been shown to have a possible link to type 1 diabetes, yet how they work isn't well understood.

This is where BABY comes in because he/she has certain genes that increase his/her risk for diabetes and he/she is eligible for this study. This study is very involved, but we are expecting that the information we gather will be very valuable in helping us learn how to prevent diabetes in the future.

S. FREQUENTLY ASKED QUESTIONS

RECRUITMENT QUESTIONS	NOTES
***Q: How do you know my child's risk for Type 1 diabetes? What did you look at?** A: When your child was born, you gave us permission to screen his/her blood for genes that have been found in people with Type 1 diabetes. We tested the blood sample and found your child to have genes that make him/her at higher risk for diabetes. However, this does not mean that your child will get diabetes. It means that his/her chances are greater than children without those genes.	
***Q: Why is my child at higher risk for diabetes? Whose fault is it?** A: No one is to blame for your child's higher risk of diabetes. Having genes that make a person at higher risk of getting Type 1 diabetes is due to the genes that a person gets from his/her mother and father. However, parents' genes can combine many different ways. Because of this, a child's genes do not look the same as his/her parents. In fact, two parents can be at a lower risk for diabetes and still have a child at higher risk for diabetes.	Also in Clinic FAQs
***Q: Where will this study be conducted?** A: LOCATION-SPECIFIC. If you have trouble getting to this location, we may be able to work with you to find a better place. We will help you to schedule all visits at times that are good for your family, and we will give you reminders.	
***Q: What is required of us if we participate in this study?** A: There are several parts to this study: • Between 3 months to 4 years of age, you will be asked to bring your child into our clinic every 3 months to collect blood samples and discuss your child's health, diet, and life experiences. At 4 years of age, these visits will be done every 6 months. • Between 3 months and 4 years of age, we will ask you to collect a monthly poop or stool sample from your child. We will give you a kit to mail the sample to us. At 4 years of age, you will be asked to do this only every 6 months. • We will give you a TEDDY Book to keep track of your child's health, immunizations, diet changes and other things you feel are important. This book will be reviewed at each clinic visit. • We will collect your child's toenail clippings at 2 years of age to test for a mineral. • We will collect water samples from your home to test for chemicals. • At some visits, we will ask you to fill out a survey to see how you feel about this study. • If your child begins to show signs of getting diabetes, we will do other tests to make sure he/she gets good care as soon as possible. Our staff is here to help you understand each part of this study. We will help to schedule visits, answer study questions, and give other support you may need.	
***Q: How long will my child be followed?**	Also in Clinic

A: This is a long-term project, planned to last up to 20 years. We would like to follow your child through puberty (15 years of age). However, you are a volunteer and you may end your child's participation at any time.	FAQs
Q: What if we move from the area within 15 years? A: TEDDY can make arrangements to monitor your child long-distance. We can gather most of the data over the phone and through the mail. The blood draw can be completed at partner labs and locations and shipped to us at no cost to you.	
***Q: Where/how/how much/how often will my child's blood be drawn?** A: We will test your child's blood during each clinic visit. From ages 3 months to 4 years of age, we will test your child's blood every three months. After that, we will test it every 6 months. We will put a cream on your child's arm to make it numb. Your child will probably not feel the blood draw at all. We will take out less than 2 tablespoons each time, which is a very safe amount. Most children do very well with the blood draw, and our nurse is very good at drawing blood from children.	
***Q: Are there any risks of participating in this study?** A: You and/or your child may feel nervous during the blood draw, or your child could get some bruises. When we share the screening results with you, you may feel worried or sad if your child is at higher risk of getting diabetes. You may have to decide if these results are something you want to share with the rest of your family or your doctor. We are here to help you understand these test results.	
***Q: Will it cost anything to be in this study?** A: No. Our study is funded by the National Institutes of Health, and we are able to provide all screening and testing for free. Some portions of the study will require a significant amount of time, In LOCATION, we will offer some compensation for your time and trouble.	
Q: What is the difference between HLA genes and autoantibodies? A: HLA genes indicate risk of developing T1DM over a person's lifetime. These markers are the same throughout your life and will not change. HLA contributes only about ¼ or 25% of the risk of getting T1DM, so it is good for screening, but the majority of people with increased risk HLA will not develop T1DM, in fact 95% of those at risk will not get diabetes. Autoantibodies are not genes. They are different since antibody markers can change over time and give us a more accurate picture of what is going on in the body right then. These antibodies can indicate the immune system is attacking cells in the body that produce insulin. However, it is important to remember that these can change over time and for reasons we don't understand yet these autoantibodies can disappear later. The HLA gene markers tell us about risk, the autoantibodies tell us if the immune system is attacking the pancreas. This is why we will want to test for autoantibodies every 3 months till age 4 and then every 6 months until the age of 15.	
Q: Will you reimburse me for my participation in the TEDDY study? A: We would like to recognize the time and travel you have put into this study, in addition to the traveling that you have done to participate. Details site specific.	

Q: What will happen to any extra blood samples you may have? A: Only if you agree to it at the time your child's blood is drawn, the blood samples may be stored for additional testing to learn more about diabetes. This information may or may not benefit you directly. We will follow all guidelines to ensure that your information is confidential.	
Q: How accurate are your tests? A: Genetic testing: When TEDDY determines that your baby has the genese that increase his/her risk for developing T1DM, we are more than 98% sure the genetic testing results are accurate. However, they cannot predict whether a person will get diabetes. Antibody testing: These results are XX% accurate, however, they can change over time, which is why we continuously test them	
Q: What happens if my child tests positive for antibodies? A: The biological markers, or autoantibodies, indicate some important changes in the body. However, they do not definitely mean that your child will go on to develop diabetes. If there are autoantibodies present, the research team will inform you of these changes and continue to monitor your child. Sometimes autoantibodies appear and then may disappear for reasons we do not yet understand. We will monitor the presence of autoantibodies and the amount within your child's blood.	
Q: What is HLA Screening? A: Human Leukocyte Antigen (HLA) screening uses either whole blood cells or a gene to identify combinations of genes that have been found more often in children with T1DM. HLA accounts for only about 50% of the genetic risk for developing T1DM.	
Q: How many children in the general population are at higher risk for T1DM? **A:** We expect to find 5% of the children screened will be at higher risk for type 1 diabetes. **(General or site specific?)**	
Q: How many children with first degree relatives are at higher risk for T1DM? **A:** We expect to find 30% of the first-degree relatives screened will be at higher risk. **(General or site specific?)**	
Q: What will you be looking for in my child's blood? A: The goal of this study is to find environmental factors that could lead to the development of T1DM. Therefore, we will be looking at a variety of factors, such as, vitamins, viruses, antibodies, and possibly other items as they are discovered to be important.	
Q: Can I have my other children tested for their risk? **A: Site-specific answer.**	
Q: If you have any new developments in diagnostic technology, would we be notified if our risk status changes? A: We will continue to keep you informed regarding your child's risk status for developing T1DM, however, some of the samples taken may not be analyzed until the end of the study and so we will not be able to make those tests results available to you.	
Q: What is the difference between T1DM and T2DM? A: Type 1 is also known as insulin-dependent or juvenile-onset diabetes and is an autoimmune disease. It typically happens in childhood or adolescence and almost never after age 35. The immune system	

inappropriately attacks the insulin producing cells until they are all gone. It is treated by injecting insulin and monitoring blood sugar levels. It is much less common than Type 2 Diabetes, which typically happens in overweight, older adults. This is not an autoimmune disease, but rather insulin is still produced, but it doesn't work anymore. It is treated through diet and exercise, oral insulin pills, and sometimes insulin injections.	
Q: Is there a cure for T1DM? What can I do? A: At this time, there is no cure for Type 1 diabetes. However, the disease can be treated with insulin injections and closely watching blood sugar levels and diet. When closely monitored, a child with diabetes can lead a long, healthy, happy life. Researchers around the world are working together with us to understand Type 1 diabetes and its causes in the hope that a cure can be developed. We encourage parents to teach good health habits such as proper diet and exercise and to have your child's health monitored closely.	
Q: Should my child avoid all sugar/sweets? A: At this time, there is no evidence that eating sugar "causes" diabetes. However, we recommend you follow your Dr's advice about diet and exercise . A normal, well-balanced diet and exercise can help prevent Type II diabetes.	
Q: Is there anything I can do now to prevent my baby from developing diabetes? Should I give them a special diet? A: Currently, there is no known method for preventing type 1 diabetes. Restricting sugar or any other diet component has not been proven to prevent diabetes. We recommend you follow your primary care physician's dietary recommendations.	
Q: How can the risk of developing diabetes be determined? A: There are two main components to developing T1DM. The first is the genetics that are inherited. This is an easy screening and will provide information about a person's chances of developing T1DM over their lifetime. However, this is only half of the picture. The rest of the risk for T1DM is determined by environmental factors that we don't completely understand at this time. What we do know is that prior to T1DM progression, the majority of people have autoantibodies develop. If your child is at increased genetic risk we will offer to do regular autoantibody screening as part of this study.	
Q: What are the signs and symptoms of T1DM? A: At diagnosis of T1DM, children often have flu-like symptoms, fatigue, increased hunger and thirst, weight loss and frequent urination. If you feel your child has these symptoms, it is very important to call your child's doctor and notify him of these signs right away. In addition, if you feel comfortable, you should mention to your doctor that your child is in the TEDDY study that follows children who have been identified as being at higher genetic risk for diabetes.	
Q: What happens if my child shows signs of developing T1D? A: The study team will tell you about these changes and continue to watch your child carefully. They will also teach you how to watch your child at home for signs of T1D.	
Q: Will you share health information from this study with my doctor?	

A: We will not share any of your child's test results or personal information unless you specifically request that we do so.	
Q: What is Type 1 Diabetes? A: MORE DETAILED ANSWER THAN FAQ's: The pancreas is an organ that lies just behind the stomach and has cells called the Islets of Langerhans, which produce insulin. When the blood sugar rises after meals, the pancreas secretes insulin into the bloodstream. This insulin is necessary to transfer sugar from the blood into cells, where it is turned into energy for the needs of the whole body. For some unknown reason, antibodies in the body can start attacking the pancreas until all the insulin producing cells are destroyed. Without insulin, the sugar is stuck in the blood and can't move into the other cells of the body, and the cells starve. The amount of sugar in the blood then rises, and glucose pours out of the body in the urine. Water and salts are lost with the glucose, the amount of urine increases, and the child is continuously thirsty. The child loses weight and becomes tired and lethargic. At this stage, treatment with insulin is needed immediately. A person with Type 1 diabetes must get insulin immediately and continue to take it throughout life. Without insulin, a person with diabetes can get very sick and die. However, with several daily insulin shots and monitoring of blood sugar levels, people with Type 1 diabetes can live normal lives.	
Q: Is there anything that can be done for my child? A: At this point, we have no strong data showing a known relationship between those things in a child's environment and the development or prevention of Type 1 Diabetes. Some things which were previously thought to contribute to diabetes (e.g., cow's milk) were later found to have no effect, and for some other things (e.g., viruses), we just don't have enough data yet to show any relationship. It takes about 10-15 years for trends to become apparent, which is why this study and your participation are very important and valuable for diabetes in the future.	
Q: There is no diabetes in our family. How can my baby be at high risk? A: Most people (90%) who develop T1D do not have a family member with the disease. The genes that increase the risk of developing diabetes can be carried through many generations without resulting in a full-blown case of T1D. Only certain combinations of genes increase a person's risk for developing T1D. Half of your baby's genes come from mom and the other half come from dad. Those genes have combined in such a way in your baby as to result in him/her having an increased risk for developing T1D.	
Q: I have older children. Could they be at risk? What about me? A: It is possible. The TEDDY study only screens children under the age of 4 months, but there are other studies, many involving the same TEDDY staff, who can do the testing for you on additional family members, free of charge. Your local TEDDY office can put you in touch with these researchers.	

Q: What are TEDDY researchers looking for? A: TEDDY is focused on searching for things in the environment that can start the diabetes process. We are collecting information about diet, viruses, medications, immunizations, pollutants and stress.	
Q: How will this study benefit my child? A: You can benefit by knowing what your child's risk for developing T1D is, and by learning what to look for. If your child does develop diabetes, participating may help with early diagnosis, which can lead to better treatment.	
Q: Are antibody tests available at my doctor? A: Some of the autoantibody tests provided in the Follow-up portion of TEDDY are available through the primary medical providers. GAD autoantibody testing is widely available, usually through specialty clinical labs. ICA512/IA2 antibody testing is generally not available, and IAA testing, while available, is generally of lower quality from commercial clinical laboratories, as compared to the IAA assays used in our study. Not all providers are aware of this type of testing, but information for clinicians is readily available in the medical literature.	
Q: Do we have to draw blood every time? A: We will try to get a blood sample at each visit in order to see if your child is showing any of the early signs of diabetes. We will offer to use a numbing cream to make it a more comfortable experience.	
Q: Why does TEDDY take so many tubes of blood? A: The study tests call for a little less than half a tablespoon, to a little less than 1 and a half tablespoons per visit, depending on age and size. It goes to many different tests, so it is spread into several tubes.	
Q: How long do you keep the information about my child? Who has access to the information? A: Since your child is at higher risk for developing Type 1 diabetes, we will keep information about your family and your child for a very long time, but no personal information (name, address, etc…) will leave this local site. We will not share your personal information, nor will we report the test results to anyone other than parents of a child unless you give us permission to do so. We will only give information about your child if you ask and sign a release of information.	
Q: Will my child's insurability be affected by these results? A: No. By law, TEDDY results should not have any effect on your child's health insurance. These tests are for research only and are considered protected information that your insurer is not entitled to review. The predictive tests tell us whether or not your child is *at increased risk for* getting diabetes over a child who does not have these genes. They cannot predict diabetes with certainty. To avoid confusion, it is wise to avoid having any information about TEDDY on your child's hospital or doctors' medical charts.	
Q: Is my child's risk considered a "pre-existing condition" for insurance purposes? A: No. The study tests are for research only, and are considered protected information that your insurer is not entitled to review. The predictive tests tell us whether or not your child *MAY* get diabetes. You can answer with honesty, that your child has no pre-existing conditions involving T1D.	

7. FOLLOW-UP STUDY RECRUITMENT

Once eligible subjects are identified and results have been communicated to the parents, the TEDDY study staff begins the process of inviting participation into the follow-up study. This recruitment process description is focused on those parents expressing an interest in the study during the conversation that communicates the HLA screening results. The training required for staff engaged in enrolling subjects in the follow-up study is part of the screening results notification training described in Section 6.

7.1. Recruitment – Telephone or Face-to-Face

In the screening results notification conversation parents are told that their child is eligible to participate in the follow-up TEDDY Study. Recruiters should ask if parents would like to hear about this opportunity then or whether it would be better to call them back. Taking the parent's needs into account is always important and this first encounter sets the tone for the study.

7.1.1 Parent expresses interest in follow-up study

Whether this is the first or subsequent conversation with the parent, all parents have been informed of the child's result, have been given further explanation as to the meaning of high risk and about T1DM. The recruiter can then begin to describe the TEDDY follow-up study. Much of what is covered in this conversation uses the same language and information that is in the informed consent for the follow-up study, but is presented in a conversational mode with time for questions and clarification. A full model script will be developed, currently the appendix material describes what the clinic visits will be like and what to expect over the years of the study.

Basic Elements of the Recruitment Conversation:

- Explain what the name "TEDDY" means and use this as a way of describing the basic aims of the study.
- Explain why it is important to study T1D in children who don't have it, but have a higher risk.
- Explain what is involved in participating in the TEDDY follow-up study. It is important that they have a real sense of what we will be asking of them and for how long.
- Invite questions about diabetes and the study, assess if they have any concerns
- Provide some explanation of the rights of research subjects
- Ask if the parent would like more information about the study or about diabetes (brochure, diabetes material)
- Ask if they want to participate.
- If so, schedule the first visit.

It is important to remember that this conversation requires sensitivity and good listening skills by the recruiter. Regardless of whether talking on the phone or in-person, it is important to talk at an easy pace (not too fast). You should check in with the parent to make sure they are still with you and understand the content of what you are saying to them. You should be sensitive to the fact that you are giving them difficult information about their newborn infant. The responsibility for clarity and understanding is with the

study staff, and the parent should never feel that they are "stupid" or "not smart enough" to understand. They should be encouraged to ask questions. The following are examples of questions and ways of checking in with the parent and should be interjected at regular intervals in the conversation.

"Did I explain that clearly?"
"Did that make sense?"
"Do you have any questions about [specify topic]?"
"Have I skipped anything?"

The frequently asked questions in the Screening Results Notification Appendix should be used as a guide in answering questions that may come up in this conversation.

7.1.1.1. Outcome: After hearing about the follow-up, parent wishes to enroll, Scheduling First Visit

The scripts below should be followed when a parent decides to participate in follow-up:

- Thank you, we really appreciate your help with the study. I need to verify that the information that we have from screening is correct.
  Baby's Name
  DOB
  Address
  Phone Number
  Cell Number
  Mom's Name
  Dad's Name

- If it would be okay, I would like to go ahead and schedule BABY NAME's first visit, This visit should be as close to when they are 3 months old as possible, which would be DATE. (SEE SCHEDULING SECTION) Because this is the first visit it will take a little longer than the usual TEDDY study visits. It will probably take about an hour and a half.

- About 2 weeks before your visit I will mail you a reminder about this visit, together with some paperwork to bring with you to the first visit. There will be a map and parking instructions so you can find us. There are also two questionnaires, one for mom and one for dad. Please fill these in and bring them with you to your first visit. If you have any questions about the forms, you can wait and fill them out at your first visit. At the first visit we will explain all of the forms and the information we will ask from you in the future. We will give you a TEDDY Book to keep track of this information. We will also show you how to collect the stool samples. We will go over the questionnaires with you. We will also explain the consent forms to you and have you sign them.

- We will mail you a letter with your child's screening results, together with a brochure about the TEDDY study, [and possibly information about diabetes, a "What Parents Can Expect" page shown in Appendix B, or other information from the local center].

- Do you have any more questions I can answer at this time? Thank you again. If you have any questions between now and then don't hesitate to call. My number is (XXX) XXX-XXXX.

7.1.1.2.Outcome: After hearing about the follow-up, parent not interested in enrolling

Here the recruiter needs to assess the parent's response and respond accordingly:

1. **Definitely not interested:**
    a. Accept this position. Ask if they have any questions and if so answer them. Explain that if they change their mind after getting the results letter, to be sure to call the study before the baby is four months old.
    b. Explain to them that it would help us to understand why people aren't interested in taking part, and could they describe their reason. Record the reasons on the contact sheet, for eventual entry onto the enrollment form.
    c. Ask them if we could contact them at a later point to see if their child has developed diabetes.

2. **Not sure and need more time to think about it:**
    a. Explain that it is not a decision that they have to make right then, and it is important for them to think about it.
    b. Explain that when they get the results letter, a brochure about the study will be included. Welcome them to call if they have questions.
    c. Also try to obtain permission for the study team to call again to see where they are with this decision.

7.1.2 Parent isn't interested in hearing about the follow-up study at this time

This should not be taken as a refusal, when expressed at the time that the results are being given and explained. Recruiters should:

- Ask if there is a better time to call back to describe the follow-up study, note this time on the contact log, and be sure to follow through.
- Tell the parent that, in the meantime, they will be getting a letter confirming these results, and giving information about the TEDDY study. They are welcome to phone us with any questions.

At the time of the follow-up call, follow the script and process described above.

If the parent does not wish to even hear about the study, then explain to them that it would help us to understand why people aren't interested in taking part, and could they describe their reason. Record the reasons on the contact sheet, for eventual entry onto the enrollment form. Remind the parent that a letter with results and study information will arrive in the mail, but we will not phone them again if they ask us not to.

7.2 Enrollment and Data Management

Local centers will develop mechanisms for tracking the contacts made for screening results notification and recruitment into the follow-up study. A model contact log form is provided in the screening results notification appendices and serves to track recruitment contacts and what is required for final disposition of an eligible subject's status.

The final status is recorded on the enrollment form on the TEDDY website. This form has fields to record the subject's study information and their enrollment status.

1. Enter the Date of Contact
    a. For subjects who enroll in the study, this is the date that the subject's parent(s) agreed to follow-up and signed the informed consent form.
    b. For subjects who refuse to be in the study, this is the date that the parent(s) indicated to the site that he/she does not want to participate in the study.
    c. For subjects who are considered passive refusals, this is the date that the TEDDY site decides that the parent(s) is not interested in enrollment.
2. Enter the Visit Location Code - this is the location where the TEDDY visit took place. Drop-down list is based upon TEDDY Clinical Center field.
3. Enter TEDDY Staff Code.
4. Select one of the following radio buttons which pertains to informing the parent(s) of the child's increased risk of developing diabetes:
    a. Date parent informed of child's increased risk (and then enter date)
    b. Date letter sent to parents (and then enter date)
    c. Parents never informed
5. The 5 options for subject's status are:
    a. Agreed to follow-up, informed consent signed:
        i. This field should not be used until the informed consent is signed, usually at the first visit.
        ii. After this option is selected and the enrollment form is saved the child's status will become "Enrolled".
    b. Subject was ineligible for follow-up because the first visit did not occur before the child was 4.5 months old:
        i. There are 5 reasons to choose from why this occurred
            1. HLA testing result not known before the child was 4.5 months
            2. Appointment not scheduled before child was 4.5 months due to scheduling problem at site
            3. Appointment did not occur within window due to circumstances beyond the site's control - this means that HLA screening results have been relayed to the parent(s), the TEDDY 3 month visit was scheduled with the parent, but the family does not show up to their 3 month visit and the visit is not able to be rescheduled within the enrollment window.
            4. Correct contact information is unavailable - this means that the TEDDY site was unable to

communicate the HLA screening results verbally to the parent(s) due to incorrect contact information.

5. Unable to contact: no response to phone calls or messages - this means that HLA screening results have been relayed to the parent(s), study information has been provided to the parent(s) by phone or mailed packet, but then the parent(s) does not respond to additional calls, messages and letters

ii. After one of the options above is selected and the enrollment form is saved the child's status will become "HLA eligible, not eligible age".

c. Subject was ineligible for follow-up because child has an illness or birth defect that precludes long-term follow-up or involves use of treatment that may alter the natural history of diabetes
   i. Site should provide description of illness or birth defect in the provided space.
   ii. After this option is selected and the enrollment form is saved the child's status will become "HLA eligible, not eligible health".
d. Subject was ineligible for follow-up because the family refused to have the child's samples stored at the NIDDK Repository.
   i. After this option is selected and the enrollment form is saved the child's status will become "HLA eligible, not eligible refused to submit samples".
e. Subject refused further follow-up:
   i. Various reasons for refusal are listed – the site should select all that apply.
   ii. After this option is selected and the enrollment form is saved the child's status will become "Not enrolled".

The model Follow-up informed consent is provided in Appendix D.

Section 7 - Appendix

A. Script describing what is involved in participating in the TEDDY Study
B. What parents can expect- short version
C. What parents can expect- long version
D. Model Follow-up informed consent

See also appendices in Section 6 - Screening Results Notification
Frequently Asked Questions for Recruitment
Model thank you letter

A. SCRIPT: WHAT IS INVOLVED IN TAKING PART IN THE TEDDY STUDY

The TEDDY Study will involve clinic visits with your baby. There will also be things for you to do at home. The clinic visits will be 4 times a year (every 3 months) starting when child name is 3 months old until they are 4 years old. After this, for most children the clinic visits will be twice a year until he/she is 15 years old , some children will continue to be seen every 3 months until the age of 15 years old.

At these clinic visits we will gather the information that you have been keeping track of in the book we call the TEDDY Book. We will also do diet records with you. Between the clinic visits, we will ask you to write down everything that your child eats for 3 days. During the clinic visit we will go over all this information with you, and ask some more questions about your child's health and experiences. At the clinic visit we will measure and weigh your child, take a nasal swab sample and take a blood sample. The blood tests will tell us if your child might be getting diabetes. Before children develop Type I diabetes, their body starts to make antibodies against the insulin cells in the pancreas. By looking for these antibodies in the blood we can tell if there is an autoimmune process starting and if your child may be developing diabetes. We will take blood from a vein in child name arm or hand. We do use a numbing cream (EMLA) so that your child won't feel the needle. Babies don't always like to stay still so sometimes there is fussing, but the blood test itself will not be painful.

The tests that we do are very specialized. They are not tests that are done at most doctor's offices. We will give you and only you the results of these tests. If your child does have any of the antibodies, we will let you know. Right now there is no way to stop getting the disease. However, for children that have taken part in studies like this one, their diabetes has been caught very early, and they did not get as sick as they would have. There may also be prevention studies in the future that your child can do if he/she does get antibodies.

In addition to the clinic visits we will ask you to send us monthly samples of your baby's stool (poop) until your child is age 4, then four times a year until age 10 and then twice a year until age 15. The reason for stool samples is that this is the best way to tell if viruses that have been in the stomach or intestines. These viruses may speed up getting diabetes. These viruses pass through the body quickly, so the best way to tell if someone has such a virus is to test their stool often. The tests are easy. We will give you clean collection containers and postage-paid envelopes to mail the stool to our lab.

We know that this study will take a great deal of time and effort on your part. To thank you for helping us learn more about this very serious childhood disease and to reimburse you for your time and effort, we will also pay you $____ for each clinic visit you and your child come to, and $___ for each stool sample that you mail in.

B. WHAT PARENTS CAN EXPECT-Short Version

Below is a list of activities you will be asked to do for the TEDDY study. You will get a more detailed list at your first clinic visit.

TEDDY STUDY - What Parents Can Expect

First Clinic Visit (when baby is 3 months old)

- ❑ Complete Informed Consent
- ❑ Baby's blood drawn
- ❑ Baby's height and weight measured
- ❑ Interview and review of mailed questionnaires
- ❑ Instruction on:
  - 3-day diet record
  - Using the TEDDY Book
  - Sending baby's poop (stool) sample by mail

Clinic Visits when your baby is 6, 9, 12, 15, 18, 21 24, 27 months old*

- ❑ At every clinic visit
  - Baby's blood drawn
  - Baby's height and weight measured
  - Collection of part of TEDDY Book
- ❑ At some clinic visits
  - Collection of 3-day diet record
  - Complete various questionnaires (about child's food, illnesses, pets, and life stresses)
  - Nasal swab sample collection (collected at the 9 month visit and beyond)
  - Child's toenail clippings (24 month visit only)
  - Test for Celiac disease (included in blood draw at 24 months)

Clinic visits when child is 30-48 months old*

- ❑ Every 3 months:
  - Child's blood drawn
  - Child's height and weight measured
  - Nasal swab sample collection
  - Collection of part of TEDDY Book
- ❑ Every 6 months:
  - Collection of 3-day diet record
- ❑ Once a year:
  - Parent questionnaire
  - Test for Celiac disease (included in blood draw)
  - Salivary sample collection (42 month visit)
  - Toenail sample collection (48 month visit, collected every 2 years)

Clinic visits when child is 54 months old – 15 years old* (most children will be seen twice a year until he/she is 15 years old , some children will continue to be seen every 3 months until the age of 15 years old)

- ❑ Every 6 months:
  - Child's blood drawn
  - Child's height and weight measured
  - Collection of 3-day diet record
  - Nasal swab sample collection
  - Collection of part of TEDDY Book
- ❑ Once a year:
  - Parent questionnaire
  - Child questionnaires (starting when child is 10 years old)
  - Test for Celiac disease (included in blood draw)
  - Salivary sample collection (54 month visit and 66 month visit)
  - Toenail sample collection (from 6 year visit collected every 2 years)

At Home Activities when child is 3 months old – 15 years old

- ❑ Mail child's poop sample
  - Every month when child is 3-48 months old
  - Every 3 months when child is 4-10 years old
  - Every 6 months when child is 10-15 years old
- ❑ Do 3-day diet record & keep TEDDY Book up-to-date
- ❑ Collect tap water sample and bring to 9 month visit, 36 month visit, 5 year visit, 7 year visit, 9 year visit, 11 year visit, 13 year visit and 15 year visit.

***If child develops autoantibodies, these things will be added to clinic visits:**

- □ Every 3 months: test blood sugar level
- □ Every 3 months: test HbA1c level (child must be at least 12 months old)
- □ Every 6 months: Oral glucose tolerance test (child must be at least 36 months old)

C. WHAT PARENTS CAN EXPECT- Detailed long version

When baby is 2 Months Old (30-40 minutes to complete forms)

- First 2 Questionnaires are mailed to you. Please fill them in, and bring to 3-Month Visit.

3 Month Visit to Clinic (60-90 minutes)

- Informed Consent form discussed, questions answered, and form signed.
- Small amount of blood will be drawn from baby
- Baby's height and weight measured
- We will teach you how to do a 3 day dietary recall of your baby's diet
- We will introduce you to the TEDDY Book
- We'll teach you how to send child's poop (stool) by mail– we provide container/postage
- Interview and review of mailed questionnaires

When baby is 3-27 months old

- You mail us a sample of your child's poop once a month – we'll provide instuctions, container, postage

6 Month Visit to Clinic (45 minutes)**

- Small amount of blood will be drawn from baby
- Baby's height and weight measured
- Collection and discussion of 3 day diet record and sections of TEDDY book (both completed before the clinic visit)
- We will complete the Parent Questionnaire with you

9 Month Visit to Clinic (45 minutes)**

- You bring a sample of your tap water – we will provide the container
- Small amount of blood will be drawn from baby
- Baby's height and weight measured
- Collect and discuss the 3 day diet record and sections of TEDDY book (fill both in before the clinic visit)
- We will complete the Demographic/Family History Questionnaire with you
- Nasal swab sample will be collected from baby

12 Month Visit to Clinic (30 minutes)** #

- Small amount of blood will be drawn from baby
- Baby's height and weight measured
- Collect and discuss the 3 day diet record and sections of TEDDY book (both filled in before the clinic visit)
- Nasal swab sample will be collected from baby

15 Month Visit to Clinic (30 minutes)** #

- Small amount of blood will be drawn from baby
- Child's height and weight measured
- Complete the Parent Questionnaire
- Collection and discussion of sections of TEDDY book (completed before the clinic visit)
- Nasal swab sample will be collected from baby

18 Month Visit to Clinic (30 minutes)** #

- Small amount of blood will be drawn from baby
- Child's height and weight measured
- Collect and discuss a 3 day diet record and sections of TEDDY book (both filled in before the clinic visit)
- Nasal swab sample will be collected from baby

21 Month Visit to Clinic (30 minutes)** #

- Small amount of blood will be drawn from baby
- Child's height and weight measured
- Collect and discuss sections of TEDDY book (filled in before the clinic visit)
- Nasal swab sample will be collected from baby

24 Month Visit to Clinic (30 minutes)** #

- Small amount of blood will be drawn from baby
- Child's height and weight measured
- We will clip your child's toenails and keep a sample of this.
- Collect and discuss a 3 day diet record and sections of TEDDY book (both filled in before the clinic visit)
- We will test for risk of celiac disease using the blood already drawn from the baby
- Nasal swab sample will be collected from baby

27 Month Visit to Clinic (30 minutes)** #

- Small amount of blood will be drawn from baby
- Child's height and weight measured
- Complete the parent questionnaire
- Collection and discussion of sections of TEDDY book (completed before the clinic visit)
- Nasal swab sample will be collected from baby

From baby's 28th Month – 48th Month (20-30 minutes per visit)** #

- Once a month, you mail us your child's poop sample– we'll provide container, postage
- Once every 3 months attend a clinic visit in which a small amount of blood will be drawn from the child and child's height and weight measured, collection and discussion of sections of TEDDY book (completed before the clinic visit) and a nasal swab sample will be collected from the child
- Once every 6 months collection and discussion of 3 day diet record (completed before the clinic visit)
- Once a year, complete the parent questionnaire
- Once a year we'll test your child for celiac disease risk in the blood already drawn.
- You bring a sample of your tap water to the 36 month visit– we will provide the container
- When your child is 3 ½ years old complete the Child Behavior Checklist
- When your child is 3 ½ years old we will collect a salivary sample

From the 36th Month onwards, if your child DOES develop signs that his/her insulin-making cells are being destroyed: Once every 6 months, at a clinic visit, we will give your child a special test called an Oral Glucose Tolerance Test to see if your child is developing diabetes. We will draw some blood from your child, give your child a sweet drink and then draw some

more blood 2 hours later. We will numb your child's arm with a special cream before we do this.

From the 48th Month to 15 Years Old (30 min per visit)** #

- Once every 6 months attend a clinic visit in which a small amount of blood will be drawn from the child and your child's height and weight measured and a nasal swab sample will be collected from the child (for some children, all of these will be done once every 3 months)
- When child is 4-10 years old once every 3 months, you mail us your child's poop sample, when child is 10-15 years old once every 6 months, you mail us your child's poop sample– we'll provide container and postage
- Once every 6 months, we collect and discuss a 3 day diet record and sections of TEDDY book (both filled in before the clinic visit; for some children the TEDDY Book will be collected and discussed once every 3 months)
- Once a year complete the parent questionnaire
- Once a year, we will test your child for a marker of celiac disease
- When the child reaches 10 years old, once a year, you and your child will fill in the child questionnaire.
- Starting at the 4 year visit every two years we will clip your child's toenails and keep a sample of this.
- Starting at the 5 year visit every two years you bring a sample of your tap water to the clinic visit– we will provide the container
- When your child is 4 ½ and 5 ½ years old complete the Child Behavior Checklist
- When your child is 4 ½ and 5 ½ years old we will collect a salivary sample

**If child develops autoantibodies we will test your child's blood sugar level every 3 months

#If child develops autoantibodies we will test your child's HbA1c level every 3 months

D. Model Follow-Up Informed Consent

IRB#

Informed Consent to Participate in Research and Authorization for Collection, Use, and Disclosure of Protected Health Information

You are being asked to take part in a research study. This form provides you with information about the study. The Principal Investigator (the person in charge of this research) or a representative of the Principal Investigator will also describe this study to you and answer all of your questions. Before you decide whether or not to take part, read the information below and ask questions about anything you do not understand. Your participation is entirely voluntary. And you can refuse to participate without penalty or loss of benefits to which you are otherwise entitled.

1. Name of Participant ("Study Subject")

_____

2. Title of Research Study

The Environmental Determinants of Diabetes in the Young (TEDDY) Study
Part 2: Follow up

3. Principal Investigator(s) and Telephone Number(s)

Co-Principal Investigator(s)

Co-Investigator(s):

Research Coordinator:

Research Nurses:

4. Source of Funding or Other Material Support

National Institutes of Health, USA

5. What is the purpose of this research study?

Your child is being asked to join a study to help determine what causes type 1 diabetes mellitus (T1DM). T1DM used to be called childhood diabetes or insulin-dependent diabetes. T1DM occurs when special cells in the body, called the beta cells of the pancreas, are destroyed by the body's infection fighting cells, called immune cells. Evidence that these cells are being destroyed is seen by the presence of antibodies against the beta cells in the blood called autoantibodies. When these beta cells are destroyed, the body can not make the

chemical insulin. Insulin is needed for the body to use food. Insulin helps keep the sugar level in the blood normal. If there is no insulin in the body, the sugar in the blood becomes high and this makes someone get sick. When a child develops T1DM, they must take insulin by shots or pumps every day to stay well.

Research tells us that children who get diabetes have certain kind of genes. Other children who have these genes are at higher risk for getting diabetes. However, not all children who are higher risk get diabetes. We think that something happens that "triggers" or causes a child with higher risk genes to actually get diabetes. It is the purpose of this study to try and find out what are the triggers that cause children to get diabetes.

Six groups of research doctors from across the world are working together in this study. All of the centers are following children with higher risk genes. All of the centers are going to get the same information about the lives of the children in the study. Your child has been found to have higher risk genes. We would like to follow your child in our search for what triggers diabetes. We would like to test and keep track of your child's diet, colds and viruses, stresses and allergies, and other life experiences. This might help us know why some people get autoantibodies and/or T1DM and others do not.

We will get a blood sample on your child every 3 months for 4 years. After that, your child will be seen every 6 months until your child is 15 years old. We will test your child's blood for a number of things, and we will also test your child's stool and nasal swab samples. We will test your child's blood for a reaction against the beta cells, called autoantibodies. We will test your child for 3 different autoantibodies. The presence of one or more of these autoantibodies means the immune cells are attacking the beta cells and that the beta cells might be destroyed. This might lead to diabetes. However, not all children who get autoantibodies will get diabetes. We will compare the life experiences and blood and stool tests of the children who get autoantibodies and diabetes with some of those children who do not get autoantibodies or diabetes. In this way we hope to find the triggers of T1DM in children with a high-risk gene. In the future, this information will be used to try to prevent diabetes in other children.

6. What will be done if you take part in this research study?

If you agree to be in the study, we will send you some questionnaires. We will ask questions about your pregnancy and how you feel about being in the TEDDY study.

When we first see your child, we will give you a special TEDDY book. This book will help you keep track of your child's life experiences. We will ask you to write things down in the TEDDY book and bring it with you to your study visits. We will also teach you how to keep a diary of everything your child eats for three days. We will ask you to do these 3-day diet records every 3 months for 1 year. We will ask you to do this every 6 months after that.

When we see your child we will take a small amount of blood, 2 tablespoons or less. All the tests, how often they are done and how long each visit should take are shown in the accompanying attachment. We will use this blood to see if any of the cells in your child's

body that make insulin are being destroyed. We can use this blood to see if your child has been sick or exposed to various things. We can use the blood to see your child's level of vitamins and minerals.

All children's blood samples will be tested for autoantibodies at each visit (signs that the beta cells that make insulin are being destroyed). Only some children's blood samples will be tested for signs of illness or level of vitamins or minerals. Most of the tests will be done at the end of the study. Other children's blood samples will never be tested for signs of illness or level of vitamins or minerals.

We will also take blood from the child's mother if she is diabetic or had gestational diabetes, or if your child tests positive for autoantibodies in the first six months of life.

Every month we will ask you to send us a sample of your child's poop or stool . We will give you a special package to send us the sample. You will not have to pay the postage. We can use the stool samples to test for certain kinds of illnesses.

Sometimes we will ask you to fill out more questionnaires. During the first two years we will ask you to fill out questionnaires two times a year. After that, we will ask you to fill out questionnaires once a year. The questions ask about how you are feeling and your reactions to the study.

When your child is 9 months old we will begin collecting nasal swab samples.

When your child is 9 months old, 3 years old, and every two years after that through the life of the study we will ask for a water sample from your home to test for minerals.

When your child is 2, we will trim your child's toenails. The toenail clippings can be used to test for minerals in your child's body. When your child is 2 we will also use some of your child's blood to test for a marker of celiac disease. Children with celiac disease get sick when they eat gluten, something that is in grains like wheat, rye, barley and oats. The same genes that makes a child at-risk for diabetes can make a child at-risk for celiac disease. We will look for the celiac disease marker once a year from the time your child is 2 until the end of the study. If we find it, you will tell your child's doctor so your doctor can do some additional tests to see if your child has the disease. Celiac disease can be treated by a special diet.

At 3 ½, 4 ½ and 5 ½ years of age you will complete a questionnaire called the Child Behavior Checklist.

In Europe, at 3 ½, 4 ½ and 5 ½ years of age a salivary sample will be collected from the child.

We may look at your child's medical records throughout the study. This is called protected health information. It can include health records, genetic, blood, stool, or urine tests, and family histories. At the end of this consent form, we will ask your permission to collect your child's protected health information.

What will happen if your child develops autoantibodies?

About one in 20 study children will develop one autoantibody. An autoantibody is a sign that beta cells making insulin are being destroyed. If this happens to your child, we will test your child's blood for T1DM every time we see your child.

About one in 40 children in the study will develop two or more autoantibodies. Autoantibodies are a sign that the beta cells making insulin are being destroyed. If this happens to your child, and your child is over 3 years of age, we will give your child a special test called an Oral Glucose Tolerance Test every 6 months. We will ask your child not to eat breakfast the morning of the test. We will give your child a sweet drink. We will then take ½ teaspoon of blood every 30 minutes for 2 hours. We do not want to stick your child many times to get this blood. So we will put a small tube into your child's arm and take the blood from the tube. We will numb your child's arm with a special cream before we put the tube in the arm.

Informed Consent and Assent

As your child's parent, you must consent to have your child participate in the TEDDY study. Because the study could last until your child is 15 years old, we will ask you for your permission for your child to be in TEDDY every 5 years (at 5 years and 10 years of age). When your child is 7 years old, we will ask for your child's assent or agreement to continue in the study. When your child is 10 years and 15 years old, we will again ask your child for assent or agreement to be in the study.

7. What are the possible discomforts and risks?

Before we take your child's blood we will use a special numbing cream. Many children do not feel much when we get blood after using this special cream. Some children do not like it. Some children cry. There could be a bruise or swelling or infection. The risk of infections is small.

If your child needs an Oral Glucose Tolerance Test, your child must miss breakfast the morning of the test. Some children do not like missing breakfast. Some children do not like the taste of the sweet drink we give during the test. Some children find it hard to stay quiet for 2 hours until the test is done. Putting the small tube into the child's arm may hurt. There could be a bruise or swelling or infection. The risk of infection is small.

You may be upset or worried about your child. However, most of the children in this study will not get T1DM. You may get upset if your child develops an autoantibody, a sign that the beta cells making insulin are being destroyed. We will fully explain the meaning of each test result. You may ask questions at any time.

Some people worry that their child might be denied health insurance or life insurance. To protect your child, we will not tell anyone else about your child's participation in this study. We will keep all of the information about your child in locked files. Your baby will be given a number so names will not be used. Only members of the TEDDY study team will be able to use the locked files. No information will be put in your child's medical record by the study personnel. You may want to talk about the study with your child's physician. However, we suggest study information not be placed in your child's medical record.

D. We want to answer all of your questions. We are here to answer your questions today. Later, you may think of other questions. Please call the Principal Investigator ……..or the Coordinator…….. or …….(Site specific) **if there is anything you want to discuss.**

8a. What are the possible benefits to you?

We will tell you any new information we learn about what causes T1DM. We will tell you about any studies to prevent diabetes that might be right for your child. If your child got T1DM, we might find it quicker. We will tell you about any studies for children with newly diagnosed T1DM.

We will also tell you if your child has a marker for celiac disease. If you child has celiac disease, this testing may help you find the disease earlier and get it treated sooner.

8b. What are the possible benefits to others?

The results of this study will help us understand why some children with the high-risk gene get T1DM while other children with the same gene do not. When we understand the things that can trigger T1DM, we can develop new studies to try and prevent the disease.

9. If you choose to take part in this research study, will it cost you anything?

No

10. Will you receive compensation for taking part in this research study?

Each time we see your baby we will give you $20.00. This money will help pay for your gas, transportation or parking. **(Site specific)**

11. What if you are injured because of the study?

If your child is injured by a study procedure, only professional medical care that you receive at …… will be provided without charge. Hospital expenses will have to be paid by you or your insurance provider. **(Site specific)**

12. What other options or treatments are available if you do not want to be in this study?

You are free not to participate in this study. If you choose to participate, you are free to withdraw your consent and drop out at any time without this decision affecting your medical care.

13a.Can you withdraw from this research study?

You can drop out of this study at any time. There are no penalties for dropping out. You will not lose any benefits you are entitled to.

If you decide to drop out, you should contact ……..…..at…….…… .

If you have any questions regarding your rights as a research subject, you may phone the Institutional Review Board (IRB) office at……...

13b.If you withdraw, can information about you still be used and/or collected?

If you drop out of the study, we will not collect any more information from you or your child. However, information we got before you dropped out may be used. Your child's name will never be used

13c.Can the Principal Investigator withdraw you from this research study?

You may be taken out of the study if you do not meet the study requirements. You may be taken out if the TEDDY study team thinks the study would do you or your child harm. The National Institutes of Health is paying for the study. It can stop the study at any time.

14. How will your privacy and the confidentiality of your Protected Health Information be protected?

Your child's health records are considered protected health information. These health records can include results of medical exams, blood, genetic, stool, or urine tests, and family histories. Only members of the TEDDY study team and the Institutional Review Board have the legal right to see your research records. We will not show your research records to any one without your permission.

When we talk about the study at scientific meetings, we will never use your name or your child's name. When we write about the study in scientific journals, we will never use your name or your child's name.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Even with the Certificate of Confidentiality, the investigators continue to have ethical and legal obligations to report child abuse or neglect and to prevent you from carrying out any threats to do serious harm to yourself or others. If keeping information private would immediately put you or someone else in danger, the investigators would release information to protect you or another person.

DHHS personnel may request identifying information for purposes of performing audits, carrying out investigations of DHHS grant recipients, or evaluating DHHS funded research projects.

15. If you agree to participate in this research study, what Protected Health Information about you may be collected, used and disclosed (given) to others?

As part of this study, some of your child's health information will be collected, used, and shared with the TEDDY study team. This information is considered protected health information and includes your child's family history of T1DM, your child's growth records, the results of genetic, blood, stool, and urine tests.

16. For what study-related purposes will your Protected Health Information be collected, used and disclosed to others?

The study will try and find out why some children with the high-risk gene get T1DM and other children do not. To answer this question, we need to follow children with the high-risk gene. We will collect a lot of information about these children. Some of the children in the study will get T1DM. Most of the children will not. We will compare the life experiences of the children who get T1DM with the life experiences of children who do not get T1DM. This way we hope to find the triggers of T1DM in children with the high-risk gene. We will then use this information to try and prevent the disease.

17. Who will be authorized to collect, use and disclose to others your Protected Health Information?

Members of the TEDDY study team may collect, use, and share your Protected Health Information.

18. Once collected or used, who may your Protected Health Information be disclosed to?

Your Protected Health Information may be given to:

- The National Institutes of Health which is paying for the study
- Government agencies responsible for overseeing research. These agencies may include the Food and Drug Administration, the Department of Health and Human Services, and the Office of Human Research Protections
- Government agencies responsible for overseeing public health. These agencies may include the Centers for Disease Control and Federal, State and local health departments
- Institutional Review Board
- TEDDY researchers

19. If you agree to participate in this research, how long will your Protected Health Information be collected, used and disclosed?

Your Protected Health Information could be used or shared for many, many years. Right now, we do not know when the study will end.

20. Why are you being asked to authorize the collection, use and disclosure to others of your Protected Health Information?

Under a new US Federal Law, researchers cannot collect, use or share your Protected Health Information without your permission.

21. Are you required to sign this consent and authorization and allow the researchers to collect, use and disclose (give) to others of your Protected Health Information?

No. You do not have to agree to be in this study. If you do not want to be in this study, it will not affect your medical care or your child's medical care.

If you want to be in the study, you must sign this consent form. You must also give your permission for the TEDDY study team to collect, use and share your Protected Health Information.

22. Can you review or copy your protected health information collected used or disclosed under this authorization?

Every 5 years and at the end of the study, you can see or copy your protected health information.

23. Is there a risk that your Protected Health Information could be given to others beyond your authorization?

We will do our best to protect your health information. We will give it only to the TEDDY study team, the Institutional Review Board, and the groups listed in item 18 above. However, it is possible that someone else could see your Protected Health Information.

24. Can you revoke (cancel) your authorization for collection, use and disclosure of your Protected Health Information?

Yes. You can drop out of the study at any time. If you drop out, no new information will be collected about you or your child. However, information we got before you dropped out may be used and shared. If you do not want us to use or share that information, you must say that in writing. Send your written request to the Principal Investigator:

25. How will the researcher(s) benefit from your being in this study?

TEDDY researchers will talk about the study at scientific meetings. They will write about the study in scientific journals. This may help their careers. This research study might lead to a new treatment or drug. The TEDDY researchers might get credit for the new treatment of drug.

26. Signatures

As a representative of this study, I have explained to the participant the purpose, procedures, possible benefits, risks, and the alternatives to being in this research study. I explained how the participant's protected health information would be collected used and disclosed:

_____

Signature of Person Obtaining Consent and Authorization Date

Parent/Adult Legally Representing the Subject. By signing this form, you voluntarily give your permission for the person named below to participate in this study. You are not waiving any legal rights for yourself or the person you are legally representing. After your signature, please print your name and your relationship to the subject.

_____

Signature of Parent/Legal Representative Date

_____

Print: Name of Legal Representative of and Relationship to Participant:

_____

Signature of Consenting 2nd Parent Date

Sample Storage

TEDDY Study samples will be stored at the local site and the central repository. Blood, stool, water and toenail clippings we collect as part of the TEDDY Study will be stored.

No personal information about you or your child will be given to the central repository. The samples in the repository are the custody of the National Institutes of Health. The samples may be used for the TEDDY Study or other research studies.

To be in TEDDY you must agree to store TEDDY samples in the central repository. You must agree to have these samples used for research.

Future Research Studies

We may want to ask you or your child to be in future research studies. Please tell us below if we may contact you. Your choice does not affect your participation in TEDDY.

YES_____ Initials _____ Please contact me about future studies.

NO_____ Initials _____ Do not contact me about future studies.

8. Administrative Procedures for Participant Scheduling

All communications with subjects that are required by the protocol must be documented in the local study records.

8.1. Initial Visit Scheduling

The first visit can occur when the baby is between 3 and 4 ½ months old. This appointment will be made by the staff member who has made contact and recruited this family's participation.

The person who enrolls the TEDDY family into the study should also make the first appointment on the phone at the time of enrollment. This person should say, "Johnny is due the week of_____ which day works for you?" as a starting point. This lets the family know from the beginning that it is important to us to see the TEDDY child as close as possible to the date he/she is due but we have to be flexible with the family's schedule. A map with the date and time of appointment will be sent with the enrollment packet.

Before scheduling an appointment, be sure that there are both clinic personnel and lab personnel available at that time. If you are booking more than one family, make sure that there are enough clinic personnel and lab personnel available for the appointment. Appointments scheduled for the initial visit need to be allotted an hour and a half in the schedule.

8.1.1 Reminder Calls

A reminder call is recommended to be made the day before the scheduled appointment. The reminder should state the time of the appointment and what to bring to that appointment, who to call to for questions/rescheduling, and confirm they have the map and parking permit.

8.1.1.1 Script for reminder calls for clinic for the initial visit:

Call each of the families with appointments for the next day.

Main Points:

- Date and time of appointment
- Map and parking permit
- Enrollment questionnaires
- Phone # for questions
- Date and time again

8.1.1.1.1 If you reach them:

"Hi this is _____ with the TEDDY study and I was just calling today to remind you about __(child's name)__'s appointment with us tomorrow at _____o'clock. I also wanted to check and make sure you have received the packet with the map and parking permit that we sent. Thank you and we'll see you tomorrow at ___o'clock.

8.1.1.1.2 For a message:

"Hi, this is a message for _(Parents Name(s))__. This is _____ calling from the TEDDY study. I am just calling today to remind you about _____'s appointment with the TEDDY study coming up tomorrow, Tuesday February 5th at _____o'clock in the morning (or afternoon). For that appointment, please be sure to use the map and parking permit that we sent and fill out and bring the paper work we sent you. If you have any questions, please feel free to give me a call back at _____. Thanks so much and we'll look forward to seeing you and _____ tomorrow February 5th at _____ o'clock."

8.2 Follow-up visits

Follow-up visits (6 month, 9 month, 12 month, etc) should be scheduled during check-in at the previous appointment. If the family refuses to schedule at that time, a clinic due sheet should but put in the basket for the scheduler with a note (example: "family could not schedule because mom's pregnant and due at that time"). The scheduler will then try to contact the family by phone to make the next appointment.

8.2.1 Reminder Call:

A reminder call is recommended to be made the day before the scheduled appointment. The reminder should state the time of the appointment and what to bring to that appointment, who to call to for questions/rescheduling, and confirm they have the map and parking permit.

8.2.1.1 If you reach them:

"Hi this is _____ with the TEDDY study and I was just calling today to remind you about __(child's name)__'s appointment with us tomorrow at _____o'clock. I'd like to remind you to fill out and bring ____'s TEDDY book with you to his/her appointment. The map is on the back of the TEDDY book and the parking permit should be in the front or back cover of the binder. Do you have any questions? Thank you and we'll see you tomorrow at ___o'clock.

8.2.1.2 For a message:

"Hi, this is a message for _(Parents Name(s))__. This is _____ calling from the TEDDY study. I am just calling today to remind you about _____'s appointment with the TEDDY study coming up tomorrow, Tuesday February 5th at _____o'clock in the morning (or afternoon). For that appointment, the map is on the back of the TEDDY book and parking permit is inside the front cover. Please fill out and bring the TEDDY book with you to ___'s appointment. If you have any questions, please feel free to give me a call back at _____. Thanks so much and we'll look

forward to seeing you and _____ tomorrow February 5th at _____ o'clock."

8.3 Cancellations, No Shows and Rescheduling

Families who do not show up or cancel their appointment should be called to reschedule their appointment. Ideally, we would prefer to have participants seen within two weeks of their due date, however this is not realistic for all families.

8.3.1 Call the participant:

8.3.1.1 If you reach them:

"Hello, this is _____ calling from the TEDDY study, is _(participants parent)_ available? (When speaking to them) Hello, how are you today? __(child's name)__ is due for his/her (3 month, 6 month, 9 month) clinic visit with the TEDDY study and I am calling today to try to get an appointment scheduled for him/her. He/She is due the week of_____. When would be a good time to bring __(child's name)__ in? (If the due date has already passed, do not say when they were due, just ask when they could bring the child in for an appointment.)…(Make the appointment)… So we have _(child's name)_ scheduled to come in to the clinic on _(appointment date)_ at _(appointment time)_. The map is on the back of the TEDDY book (or in the packet we sent at enrollment) do you have the parking permit we gave you at the last visit? (If "no" check address and send another parking permit). You will need to fill out and bring the TEDDY book questionnaires for this visit (or enrollment questionnaires) and (water sample – 9 months or when they have moved). Do you have any questions? Thank you, and we will see you on _(appointment date and time)."

8.3.1.2 For a message:

"Hello, this is _____ calling from the TEDDY diabetes study for _(parents name)_. The reason for my call today is that _(child's name)_ is due for his/her (3 month, 6 month, etc.) clinic visit with the TEDDY study and we would like to schedule that appointment at your earliest convenience. Please call us back at 303-315-____ and we can go ahead and schedule his/her appointment. Thank you and have a nice day."

When the appointment is made write the date and time at the bottom of the Clinic Due sheet and then enter it into the local databases used for clinic scheduling and tracking. One possible system for subsequent tracking would be to 1) place the call sheet in a "scheduled" binder, being sure not to shred until the family has come in to clinic. If the family is a no-show or cancels the call sheet is removed from the "scheduled" binder and moved to the "to be scheduled binder."(**Note: Individual centers will use their own way of tracking communications that may not involve binders.)**

8.3.2 Cancellations

When a family calls to let you know that they will not be able to come to their appointment, changes must be made in the TEDDY calendar, and the TEDDY tracking database. We should attempt to reschedule any cancellations at the time that they cancel. If this is not possible, the Clinic Due sheet needs to be removed from the "scheduled" binder and put in the "to be scheduled". Use the "Call the participant" section above to make the calls, but be sure to indicate during the call that you want to reschedule.

8.3.3 No Shows

When a family doesn't come to their appointment, and they haven't called beforehand to cancel the appointment, this needs to be noted and changed in the local clinic scheduling and tracking records for the participant. Use the "Call the participant" section above to call the family and reschedule the appointment. Let them know that they missed an appointment, and that you want to reschedule them. Please see the data entry section below for instructions.

8.3.4 Rescheduling

When a family calls to say they can't make it to the scheduled appointment, but they want to schedule for a different time, a new appointment should be made.

8.3.5 Study Withdrawal

Withdrawal from the study occurs when a parent actively refuses to continue participation in the study and actively requests to be withdrawn. This should be accepted and the family should be given the opportunity to have any questions or concerns addressed.

- Fill out the Change in Study Participation Form: Note all the reasons for the request to withdraw and the date of this request (see section 8.3.5.1. for form instructions; see Appendix A for example of form).
- This is the time that we would like to have the Parent Experiences Questionnaire filled in by the parents (see section 8.3.5.2. for location of Parent Experiences Questionnaire on website as well as specific instructions related to the questionnaire) – two questionnaires should be given to the family to complete – so that one can be completed by the mother (or primary caretaker) and one can be completed by the father, if applicable. If the TEDDY child is at least 10 years of age, we would also like the child to complete the Child Experiences Questionnaire at this time (see section 8.3.5.2. for location of Child Experiences Questionnaire on website as well as specific instructions related to the questionnaire). The Parent Experiences Questionnaires should be given to all families that are no longer participating in TEDDY, including those whose child develops diabetes or who choose to withdraw because their child's HLA additional genotyping results differ from the HLA screening results - making the child not eligible for the study. The Child Experiences Questionnaire should be given to all children who are at least 10 years of age and that are no longer participating in TEDDY, including those children who develop diabetes or who choose to withdraw because the

child's HLA additional genotyping results differ from the HLA screening results - making the child not eligible for the study. The staff person having this conversation should use the following points in their conversation that tells them that such a questionnaire will be coming in the mail.

- The study would appreciate having them fill out one last questionnaire that gives them the chance to tell us about their TEDDY experience and what we might do differently.
- This would be confidential and not returned to the local center, rather a stamped envelope to return it to the central data coordinating center (for US sites) and to a neutral location (for European sites) would be included. The questionnaires can also be completed online through the TEDDY Portal and will remain confidential and not seen by the local center.
- Ask if it is alright to contact the family in the future for the purposes of ascertaining disease status or for their possible interest in other studies. We would not ask or try to convince them to comeback to TEDDY. Note this response on the Change in Study Participation Form.
- Remind the family that they always have the opportunity to comeback to the study if they wish as long as the first study visit was completed before 4 ½ months of age. Families may return at any point in the study after completion of the first visit regardless of time elapsed.
- Each center should develop a final letter that should be sent to the family that includes the following points:
    - confirms their wish to withdraw from the study
    - reminds them that they are always welcomed to return
    - provides them with the signs and symptoms of T1DM.

This letter should be accompanied by the Parent Experiences questionnaire and Child Experiences Questionnaire (if the child is at least 10 years of age) and a return envelope addressed to the DCC* for US sites and addressed to the neutral location for European sites.

*Address to include on return envelopes addressed to the DCC (for US sites only):

Pediatrics Epidemiology Center
University of South Florida
Attn: Cristina McCarthy
3650 Spectrum Blvd., Suite 100
Tampa, FL 33612

8.3.5.1 Change in Study Participation Form

The Change in Study Participation Form should be used when a subject has chosen to withdraw from the study, the subject is lost to follow-up or the subject would like to rejoin the study. When one of these three reasons is selected on the form and the form is saved, the subject's participation sub-status will change to 1) Enrolled (Withdrawn) 2) Enrolled (Lost to follow-up) or 3) Enrolled (Rejoined study). If the

subject changes from "Withdrawn" to "Lost to follow-up" you should NOT note this change on the Change in Study Participation form, only on the TEDDY Update Form. If you need to change the subject's participation sub-status due to a change in the situation, you cannot make this change on the original form. You will need to use a new Change in Study Participation Form and select the new appropriate option (for changes other than from "Withdrawn" to "Lost to follow-up"). For example, if the subject's participation sub-status is 'lost to follow-up' and then the family calls and would like to rejoin the study, you cannot go back into the original form and change your selection from 'lost to follow-up' to 'rejoins study'. You will need to use a new form and select the option "Subject rejoins study as of:" If you make a mistake on the first form and accidentally save as 'lost to follow-up' and meant to indicate 'subject/family does not wish to participate further' you will need to contact the DCC to make this correction.

How to get to the Change in Study Participation Form

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject.
4. Under "Search Results", click on the Local Code of the desired subject.
5. Choose "Change in Study Participation Form" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
6. Click 'Select Form' button that is below dropdown menu.
7. Enter information
    a. 'Date of Contact' definition:
        i. If parent(s) decides he/she does not want the child to be in the study any longer and contacts the TEDDY site, this is the date that the parent(s) contacts the TEDDY site about the withdrawal.
        ii. If parent never communicates to the TEDDY site that he/she does not want the child to be in the study any longer, but starts missing visits or not answering scheduling calls, this is the date that the TEDDY site decides to withdraw the subject.
    b. 'Subject/family does not wish to participate further as of' definition:
        i. If parent(s) decides he/she does not want the child to be in the study any longer, this is the date that the parent(s) indicates that the child will be removed from the study (this may be the same date as the 'Date of Contact').

ii. If parent never communicates to the TEDDY site that he/she does not want the child to be in the study any longer, but starts missing visits or not answering scheduling calls, this is the date that the TEDDY site decides to withdraw the subject.

8. Click the Save button and close the form.

Once the Participant's Details Page has been refreshed, you will see "Change in Study Participation Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1. Click on the form link under 'Completed Additional Study Forms'
2. A new window will open which will have links to all of the "Change in Study Participation Forms" that have been saved for this subject.
3. Click on the 'view/edit/print' link to open up a specific form for this subject.

8.3.5.2 Parent Experiences Questionnaire/Child Experiences Questionnaire

How to get to the Parent Experiences Questionnaire/Child Experiences Questionnaire

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject.
4. Under "Search Results", click on the Local Code of the desired subject.
5. Choose " Parent Experiences Questionnaire" or "Child Experiences Questionnaire" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
6. Click 'Select Form' button that is below dropdown menu.
7. You can print the Teleform from here.

You will notice on the online Parent Experiences Questionnaire/Child Experiences Questionnaire that there is a "Form Status" section at the top of the form. This section consists of four radio buttons:

- Sent out (when a Parent Experiences Questionnaire is sent to both the mother and the father, only one entry of "sent out" needs to be indicated)
- Returned but not filled out
- Unable to contact (no correct address, unable to deliver mail)
- Not sent out

"Returned but not filled out" is to be used by the DCC (for US subjects) and by the designated neutral locations (for European subjects), if necessary. The other three choices are to be used by the clinical centers, if necessary.

In the Parent Experiences Questionnaire the caregiver should only indicate one answer for # 10 ("What was the worst part of the study?") and one answer for # 11 ("What was the best part of the study?"); and in the Child Experiences Questionnaire the child should only indicate one answer for # 4 ("What was the worst part of the study?") and one answer for # 5 ("What was the best part of the study?"). However we have come across instances where the caregiver/child has indicated multiple answers for each question. If multiple answers are indicated then the staff member should fill in the radio-button (bubble) next to the "Other" choice in that particular question and then indicate code WB005 ("Multiple answers were indicated for worst or best part of TEDDY") in the code box next to it.

Per the Psychosocial Committee the response to "Below, please tell us anything else you would like us to know about your experience with TEDDY" in the Parent Experiences Questionnaire/Child Experiences Questionnaire will not be translated or coded.

Once a Parent Experiences Questionnaire/Child Experiences Questionnaire has been submitted (by either the DCC for US subjects, or the neutral location for European subjects) clinical centers will see " Parent Experiences Questionnaire" and/or "Child Experiences Questionnaire" under 'Completed Additional Study Forms' near the top of the Participant's Details Page. However only the DCC will be able to open and view the submitted form. Multiple Parent Experiences Questionnaires can be submitted for each subject.

8.3.6 Passive Refusals/Withdrawal from Study

A parent may either not return calls or repeatedly not attend scheduled appointments. This situation applies to a subject where all of our known contact information (telephone and address) is thought to be accurate and these subjects can not be classified as "lost". The following approaches to these problems are suggested, but individual circumstances may require variation from these suggested approaches.

No Telephone/Mailed Contact for an already enrolled family: Attempt to contact the family 3-6 times spanning a period of at least 3-4 weeks with at least 1 call in each of the following time intervals: Weekdays 8:00 – 10:00 AM, 6:00 – 8:00 PM, and Saturday 9:00-11:00 AM. We don't want to have subjects feel like we are harassing them, but we do want them to understand that the scheduling of a visit needs to be accomplished in a specific window. Letters, instead of phone

calls could also be sent. This is a good way of verifying that the mailing address on file is still accurate. If no contact is made and no phone calls/letters returned, leave a final message that the time to schedule this particular visit is about to expire and they should contact the study clinic by a specific date if they wanted to complete some or all of the visit either by phone or in-person. You will next be calling them about the next visit in about a month (or 4 months if this is later in the TEDDY visit schedule- e.g. every 6 month schedule). Encourage the parent to call the clinic to stay in touch, even if they can't schedule this visit.

When there is repeated and consecutive "No Telephone or Visit Contact" with a family, the study staff needs to assess the feasibility of continuing to spend the extra time trying to schedule a subject who has not pursued contact with the staff.

The above protocol for trying to make contact should be followed for at least 1 year of consecutive visits prior to July 1, 2015; on or after July 1, 2015 the above protocol for trying to make contact can be followed for 2 years of consecutive visits. If the local clinic determines that there is limited gain in continuing to attempt contacting this family, then a final phone call/message using the script below should be completed and a final letter saying that because they have not had a visit in a year or more (prior to July 1, 2015) or two years or more (on or after July 1, 2015) and they have not responded to our contact attempts they are being disenrolled from the study.

- This is not an automatic withdrawal, sites will review case by case, and will base the decision on their best judgment and knowledge of the participant about appropriateness of withdrawal.
- Management of inactives is a local decision, but at a minimum should include a TEDDY Update Form (TUF).

With this letter we will also mail them a final questionnaire to assess participant experiences in the TEDDY study and reasons for dropout. The letter should stress, as above, that they are very important to the study and they are welcomed to rejoin at any time and gives the signs and symptoms of T1DM. Along with the letter, an invitation will be sent saying that they are welcome back into TEDDY in the future if they change their mind (e.g. a family member may get diabetes). The invitation will include appropriate telephone and postal contact information and a "preferred enrollment number" (the child's local code).

One month after the letter is sent if there has been no contact from the family the child is disenrolled and the "Change in Study Participation Form" should be filled out that has response 1B selected as reason for withdrawal.

NOTE: For passive withdrawals even if the site feels that they know the reason the family no longer wants to participate in TEDDY (for example – because of the blood draws), the site should not indicate this as the reason the family does not wish to participate further on the Change in Study

Participation Form. A reason should only be indicated on the Change in Study Participation Form if the family specifically communicates it as the reason for withdrawal. For instances which are considered to be passive withdrawals (a parent may either not return calls or repeatedly not attend scheduled appointments. This situation applies to a subject where all of our known contact information (telephone and address) is thought to be accurate and these subjects can not be classified as "lost") 1B should be selected on the Change in Study Participation Form.

8.3.7 Script for Final message after permission obtained to treat as a passive withdrawal is obtained:

"Hi this is _____ from the TEDDY study calling again to try and schedule (child's name) for his/her (3 month, 6 month, etc) clinic visit. We have been unable to schedule a visit for your child for over a year (prior to July 1, 2015) or over two years (on or after July 1, 2015). We would still love to schedule ____ for his/her visit but if we don't hear from you in the next two weeks we will assume you are no longer interested in participating in the TEDDY Study. If you have decided to withdraw from the TEDDY study, we hope you will call us or take the time to complete a questionnaire that you will be receiving soon in the mail. The information you share with us will help us improve the study to make it easier for you or others to continue. You can reach me at _____. Thank you and we hope to hear from you."

8.3.8 Subject consistently misses scheduled appointments

Families may be reached by telephone on a regular basis, but repeatedly miss scheduled appointments. This circumstance will not allow for adequate data and sample accrual. Subjects who miss 3 consecutive, scheduled appointments will be contacted by telephone

"Hello, this is _____ calling from the TEDDY study, is _(participants parent)_ available? (When speaking to them) Hello, how are you today? __(child's name)___ has missed TEDDY study visits in a row and I am calling today to try to see whether we should make 1 last effort to get an appointment scheduled. Missed appointments result in incomplete data, not only from your child, but also from children who could have been seen during your child's appointment slot. Sometimes parents who miss appointments want to stop participating in TEDDY, but we understand that they may be hesitant to tell us. Do you feel that way?

If they say no, then book appointment, but explain to parent that they must call us if they want to cancel it at least 24 hours before the appointment. If they no-show a 4th time follow the procedures noted above no telephone or visit contact,

If they say, they want to withdraw, attempt to ascertain all the reasons for this and fill in the Change in Study Participation Form with these responses. Tell

the family that we appreciate their participation in TEDDY, they are welcome to return at any time, and that we will send them a confirmatory letter and a Parent Experiences questionnaire and Child Experiences Questionnaire (if the child is at least 10 years of age) that is not returned to the local center.

8.3.9 Family Return after Dropout

If a family has dropped out of the study after the first visit they may return later. When a family requests to return, they may resume the study at the current point based on the child's age. A new Change in Study Participation form needs to be filled out indicating the return of the subject and the date of re-enrollment.

We will not attempt to collect all of the missed data; however, the following items should be collected.

1. Demographic information (on either 9 month Interview or Update Form for Primary Caretaker – wherever at in visit schedule when subject rejoins)
2. Family History (on either 9 month questionnaire or Update Form for Family History Questionnaire – wherever at in visit schedule when subject rejoins)
3. Immunization History
4. Current chronic illness(es)
5. Stop date of breastfeeding
6. 6 year Whole Blood Storage sample

Instructions for end dates for ongoing Chronic Illnesses, Medications, Allergies, All Special Diets and Dietary Supplements collected in the TEDDY Book:

1. Use radio button "Ended, but end date unknown" for situations in which a chronic illness/medication/allergy/special diet/dietary supplement is open, but has stopped greater than one year ago and the parent does not know the end date. This can be used for both families who rejoin and families who have never dropped out.

2. For situations in which an item is open, but has stopped less than one year ago parent should provide best estimate of stop date. This should be applied for both families who rejoin and families who have never dropped out.

3. For situations in which an item is open, but has stopped greater than one year ago and the parent DOES know the end date, TEDDY staff member should record the end date provided by the parent. This should be applied for both families who rejoin and families who have never dropped out.

Instructions for unknown start dates for ongoing Chronic Illnesses, Medications, Allergies, All Special Diets and Dietary Supplements collected in the TEDDY Book for families who rejoin:

1. For situations in which the start date for an ongoing chronic illness/ medication/ allergy/special diet/dietary supplement for a returning family is unknown the start date will be recorded as 6 months before the date of the return visit. Pursuit of medical records is always preferred.

8.4 Contact Problems Resulting in Lost-to-Follow-Up Change in Status

If a participant's telephone number has been disconnected, is a wrong number, or no one answers the phone after repeated attempts to contact them, research must be done to determine the correct telephone number for the participant. If a participant's address is incorrect, this must be researched as well by calling the telephone number(s) we have for the participant until we can verify the address information that we have on record, or get new information for the participant. Possible sources of contact information include telephone information, Internet white pages, alternate contacts, and finally a letter that might yield forwarding addresses received back on return mailings. After 1 year of no contact and indications that we do NOT have a current address or phone contacts, then this subject may be classified as "Lost to Follow-up" on the Change in Study Participation Form. All known information about the difficulty contacting a subject and the methods attempted should be noted in the local tracking databases. When new contact information for a participant is received, from any source, and it has been found to be correct, fill out a locally developed change of information form that includes the TEDDY ID number for the participant(s) affected, the name(s) of the participant(s) affected, the new information, and your name and the date. A new contact record should be entered into the local tracking database. The old record will be archived. Below are suggested resources that should be pursued before this status change is made.

8.4.1 Telephone Information (US)

411 services may be used to inquire the correct telephone number for a participant. To do this, dial 411 and then follow the voice instructions. Record any possibilities. Record the date, time and outcome of attempted contact with possible phone numbers. It is appropriate to leave a message indicating whom you are trying to contact and that you are from a research study at _____, with your telephone number, and ask them to call you back. Repeat this procedure for each possibility until you reach the correct number or all are eliminated.

8.4.2 Internet White Pages

Use the Internet white pages in a similar manner as 411 (information), recording possibilities and trying each one until the correct number is found or they are all eliminated.

8.4.3 Alternate Contacts

Alternate contacts can be found in the TEDDY Tracking database. Write down the names, phone numbers and relationship to the participant of the alternates on the Clinic or Calling Due sheet. Record on the Clinic or Calling Due sheet the date and time of each attempt to reach the alternates and indicate which alternate was called. If and when the alternate is reached, use the following script as an outline for your call.

"Hello, this is _____ from the TEDDY study, is (name of alternate) available? The reason I am calling today is that your name and number were given to us by (participant's parent's names) in the event that we were unable to contact them. Do you have their current phone number, or another way that we could reach them? Or, if you would feel more comfortable, could you get a message to them to give us a call? … Thank you so much for your time and assistance today."

8.4.4 Letter

When all of the other possible ways to contact a participant have failed, you should send them a letter indicating that you have been unable to contact them and asking them to get in touch with you as soon possible. The letter should clearly give phone numbers for them to contact, a deadline for them to contact you, and thanks for their participation in the study. Instead of that letter, a disenrollment letter may be sent to the family.

8.5 TEDDY Update Form

The TEDDY Update Form should be completed annually for TEDDY participants who have either:
1) Actively withdrawn from the study and have agreed to future contact
2) Became inactive participants by not responding to contact attempts (did not request to withdraw and were not asked about future contact)

Purpose:

1) To update diabetes, celiac disease and thyroid disease status information of inactive or withdrawn TEDDY participants
2) To update contact information of inactive or withdrawn participants
3) Assess interest in rejoining the TEDDY Study or resuming activity in the TEDDY Study

8.5.1 When to use the TEDDY Update Form

The form should be completed for all eligible past TEDDY participants (as defined above) one year after our last contact with them and annually thereafter. This contact date will be determined by the most recent date of the following: active withdrawal date, Parent Experiences Questionnaire completion date, last completed visit date, or TEDDY Update Form completion date. The TEDDY Update Form should be used annually until the child turns 15 years old, is

diagnosed with type 1 diabetes, the death of the TEDDY child, or the parents request no further contact.

8.5.2 Administration of the TEDDY Update Form

8.5.2.1 The form can be administered as an interview (in person/phone) OR as a self-administered questionnaire (mail/email).

8.5.2.1.1 As an interview:

- Fill in the date of last contact above question 3 prior to beginning the interview with the family. This date should be the last contact with the family (e.g. last visit, withdrawal date, last TEDDY Update Form).
- Explanations and questions are to be read to the primary caretaker directly from the TEDDY Update Form.
- No items should be skipped.
- If a participant refuses a question, the interviewer should note this on the interview form, initial and date.
- In the US, care should be taken to enter all dates correctly in the European format: day/month/year.

8.5.2.1.2 As a questionnaire:

- Fill in the date of last contact above question 3 prior to beginning the interview with the family. This date should be the last contact with the family (e.g. last visit, withdrawal date, last TEDDY Update Form).
- Double check that the Subject ID and Local Code on the form matches the subject prior to mailing.
- Only mail pages 1 and 2 of the form to the family (page 3 will be completed by the TEDDY study staff only)
- Include instruction sheet and black pen.
- Include a stamped self-addressed envelope to return the form to the Clinical Center

8.5.2.2 Information to be completed by study staff

On each questionnaire or interview, staff should complete information asked for in the "Office Use Only Box" located on the last page:

- "Visit Location Code" is the location where the TEDDY visit took place. Drop-down list based upon TEDDY Clinical Center field.
- If you were able to complete contact with the family complete the "Completed Contact" section:
  - "Type of Contact" is how the form was completed – mail, email, phone or in-person.
  - "Date of Interview/Date Form was Reviewed" in DD/MMM/YYYY format is the date that the interview took place or that the form was reviewed by the study staff member

  - "Form Reviewed By" is the name of the person who reviewed the answers on the form or the person who conducted the interview with the parent/primary caretaker
  - "TEDDY Staff Code" is the TEDDY Staff Code of the person who reviewed the answers on the form or the person who conducted the interview with the parent/primary caretaker
- If you were unable to establish contact with the family after multiple attempts, complete the "Incomplete Contact" section of the form. It is highly recommended that multiple contact attempts include both phone and mail.
  - "Date of Contact Attempt" in DD/MMM/YYYY format is the last contact attempt date
  - "Status of Contact Attempt" indicate the last status contact attempt by selecting 1) sent, but not returned, 2) returned, but not filled out, 3) phone contact attempted, but no response 4) unable to contact, no valid contact information (Note: an answer can be indicated under both the "Mail/Email" section and the "Phone" section, if applicable)
- If during this contact the family requests that TEDDY not contact them again indicate this in the corresponding checkbox in the section entitled "PERMISSION TO CONTACT".
- Additional follow up contact should be made to all families that answer yes to diabetes or celiac disease. A diagnosis form(s) should be completed and a copy of the medical record relating to diagnosis should be obtained.

NOTE: If you plan to submit the TEDDY Update Form through Teleforms please be sure to cover the "Current Contact Information" on page 1 of the form with sticky notes before scanning the form. This box contains information that the DCC cannot receive.

8.5.2.3 How to get to the TEDDY Update Form

1) Logon to the TEDDY website http://teddy.epi.usf.edu/
2) Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3) Search for the desired subject
4) Under "Search Results", click on the Local Code of the desired subject.
5) Choose "TEDDY Update Form" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
6) Click 'Select Form' button that is below dropdown menu.

7) You can print the Teleform from here and/or enter information, click the Save button and close the form.

Once the Participant's Details Page has been refreshed, you will see "TEDDY Update Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1) Click on the form link under 'Completed Additional Study Forms'
2) A new window will open which will have a link to the "TEDDY Update Form" that has been saved for this subject.
3) Click on the 'View/Edit/Print" link to open up the specific form for this subject.

Section 8 – Appendix

A. Change in Study Participation Form
B. TEDDY Update Form

A. Change in Study Participation Form

TEDDY
The Environmental Determinants of Diabetes in the Young

Change in Study Participation

* These fields are required in order to SAVE the form.

Subject ID		Date of Birth	
Local Code		Date of Registration	
Status		Clinical Center	

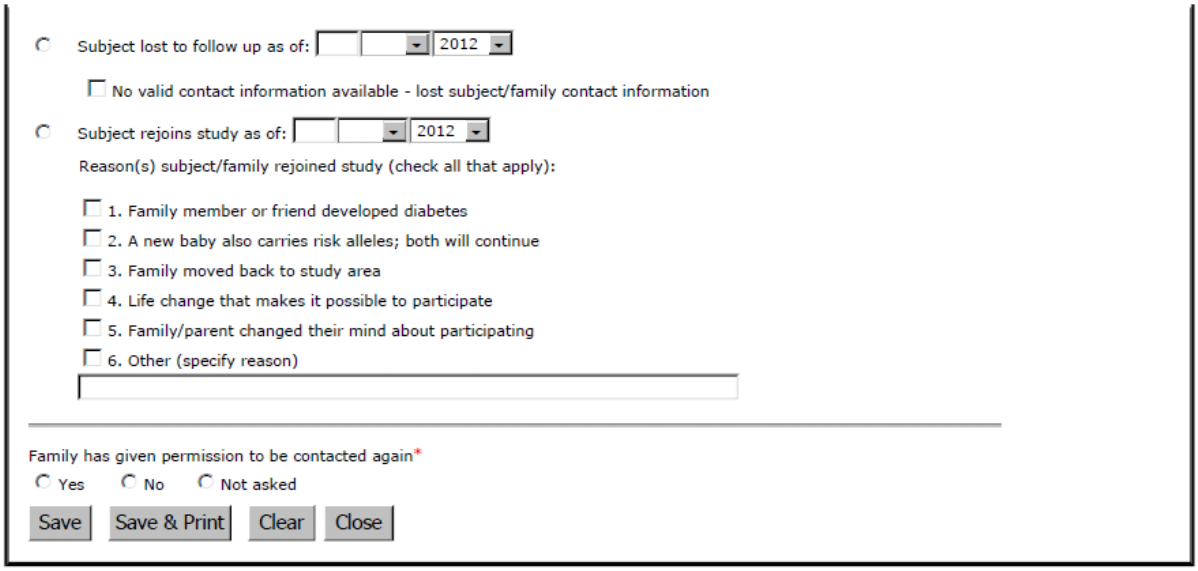
Date of Contact	2012 *	Visit Location Code	*
TEDDY Staff Code	*		

○ Subject/family does not wish to participate further as of: 2012

Who is declining the participation? ○ Parent ○ Child ○ Both

Reason(s) subject/family does not wish to participate further (check all that apply):

1. No reason given
   - ☐ A. Active Contact Made, subject asked to be withdrawn from study, no reason given
   - ☐ B. Passive Withdrawal: active contact NOT made, contact information correct, subject not responding to repeated scheduling attempts.
2. ☐ 2. Unavailable - moving out of the area
3. ☐ 3. Wants to 'wait and see' - will deal with diabetes if it occurs
4. Protocol characteristics
   - ☐ A. Concerns about blood draw
   - ☐ B. Concerns about poop samples
   - ☐ C. Concerns about frequency of visits
   - ☐ D. Concerns about filling out questionnaires/forms
   - ☐ E. Protocol too demanding
   - ☐ F. Duration of study is too long
   - ☐ G. Doesn't want to be reminded of the child's risk
   - ☐ H. Transportation difficulties, too far to travel
   - ☐ I. Worried about privacy/confidentiality
   - ☐ J. Worried about future loss of insurance
   - ☐ K. No prevention or treatment is offered
   - ☐ L. Food diaries too troublesome
   - ☐ M. Other (specify reason:)
5. Family characteristics
   - ☐ A. Too busy/not enough time
   - ☐ B. Feeling overwhelmed/too stressed
   - ☐ C. Language barrier
   - ☐ D. Child has other medical or behavioral problems
   - ☐ E. Parent or other family member has medical or emotional problems
   - ☐ F. Family members can't agree on whether to participate
   - ☐ G. Doesn't want to be in research
   - ☐ H. Subject already in another research study
   - ☐ I. Family member already in another research study
   - ☐ J. Family health care provider does not recommend participation
   - ☐ K. Other (specify reason:)
6. ☐ 6. HLA additional genotyping sample result differs from HLA screening result: child is not HLA eligible for the study, family no longer wants to participate
7. ☐ 7. TEDDY child no longer wants to participate


Subject lost to follow up as of: 2012
No valid contact information available - lost subject/family contact information
Subject rejoins study as of: 2012
Reason(s) subject/family rejoined study (check all that apply):
1. Family member or friend developed diabetes
2. A new baby also carries risk alleles; both will continue
3. Family moved back to study area
4. Life change that makes it possible to participate
5. Family/parent changed their mind about participating
6. Other (specify reason)
Family has given permission to be contacted again*
Yes
No
Not asked
Save
Save & Print
Clear
Close

B. TEDDY Update Form

26761

Local Use Only

SubjectID

Dear TEDDY Study Participant,

It has been more than a year since our last contact with you. We really appreciate your participation in the TEDDY Study, and we would like to keep in touch with you.

TEDDY has become one of the most important type 1 diabetes studies in the world. Your participation provided some very useful information for our study, and as we get closer to understanding the causes of type 1 diabetes it is important for us to learn if there are any new developments related to diabetes in your family.

Please take a few moments to update your contact information and complete the short questionnaire. The more we learn from our TEDDY families, the closer we get to discovering the causes of diabetes. As always the TEDDY Study will keep information confidential and it will only be used for study purposes in summary form.

Thank you for everything you have done for the TEDDY Study. We look forward to keeping in touch with you.

Having updated contact information will be a great help to us in trying to keep in touch with you. Please fill in the box below to help keep our records up to date.

CURRENT CONTACT INFORMATION:

Telephone: _____ O home O work O cell who: _____

Telephone: _____ O home O work O cell who: _____

Email: _____

Address: _____ Unit#: _____

City: _____ State: _____ Zip Code: _____

26761

Local Use Only

SubjectID

TEDDY Update Form

As an inactive or past TEDDY Study participant it is still important for us to know whether your child has developed diabetes or celiac disease.

1. Date you completed this questionnaire: ☐☐ / ☐☐☐ / ☐☐☐☐
(DD/MMM/YYYY - *Example 01/JAN/2010*)

2. What is your relationship to the TEDDY child?
○ Mother ○ Father ○ Other Primary Caretaker ○ Other (specify) _____
Code (office use only) ☐☐☐☐☐

We last had contact with you on: ☐☐ / ☐☐☐ / ☐☐☐☐
(DD/MMM/YYYY - *Example 01/JAN/2010*)

Keep this date in mind for the following questions.

3. Since our last contact with you, has your child been diagnosed with type 1 diabetes?
○ Yes ○ No

IF YES:
a. What was the date of diagnosis of diabetes? ☐☐ / ☐☐☐ / ☐☐☐☐
(DD/MMM/YYYY - *Example 01/JAN/2010*)

b. If your child has been diagnosed with diabetes, has insulin been started?
○ Yes ○ No ○ Unknown

4. Since our last contact with you, has your child been diagnosed with celiac disease?
○ Yes ○ No

IF YES:
a. What was the date of diagnosis of celiac disease? ☐☐ / ☐☐☐ / ☐☐☐☐
(DD/MMM/YYYY - *Example 01/JAN/2010*)

5. Since our last contact with you, has your child been diagnosed with thyroid disease?
○ Yes ○ No

IF YES:
a. What was the date of diagnosis of thyroid disease? ☐☐ ☐☐☐ ☐☐☐☐
(DD/MMM/YYYY - *Example 01/JAN/2010*)

Sometimes circumstances change where inactive participants are interested in re-engaging in regular TEDDY visits or past participants are interested in re-joining the TEDDY Study.

6. Would you like to have TEDDY contact you about re-activating or re-joining?
○ Yes ○ No

THANK YOU FOR TAKING THE TIME TO STAY IN TOUCH

26761

Local Use Only

SubjectID

Office Use Only

Local Code: **Clinical Center:**

Subject ID: **Visit Location Code:**

COMPLETED CONTACT:

Type of Contact: ○ Mail ○ Email ○ Phone ○ In Person

Date of Interview/Date Form was Reviewed: ___/___/___
(DD/MMM/YYYY - *Example 01/JAN/2010*)

Form Reviewed By: _____ **TEDDY Staff Code:**

INCOMPLETE CONTACT:

Date of Contact Attempt: ___/___/___
(DD/MMM/YYYY - *Example 01/JAN/2010*)

Status of Contact Attempt: **Mail/Email**

○ Sent, not returned

○ Returned, not filled out

Phone

○ Contact attempted, no response

○ Unable to contact, no valid contact information

PERMISSION TO CONTACT:

○ Participant requested NO FUTURE CONTACT (check this only if the family requests that we not contact them again)

ONE TIME BLOOD DRAW:

○ Yes, accepted ○ No, refused ○ Not offered

TEDDY Update Form Page 3 of 3 Form Revision Date: 8 August 2017

9 Overview of Clinic Visits

TEDDY Study clinic visits are the primary, though not the only, data collection point. These visits are also the opportunity for engaging parents and TEDDY children in the long term mission of the study, for monitoring autoimmune and T1D symptoms, and for providing support to families with high risk children. A summary of the TEDDY visit schedule and the data contents is described in Table 9.2

9.1 Visit Schedule, Scheduling Windows and Missed Visits

As part of the recruitment discussion, parents are informed of what to expect if they choose to participate in the study. Once a child has enrolled and completed the first (3 month) visit a scheduling routine will need to be established.

- Children will be enrolled and seen for the first visit at the age of 3 months and no later than the age of 4 ½ months.
- Participants will then be asked to attend a clinic visit at 3 month intervals through 48 months of age.
- At 4 years of age and beyond those children who have been deemed persistent autoantibody positive will follow a 3 month visit schedule (confirmation results from the confirmatory Autoantibody lab will not be taken into consideration for determining the subject's visit schedule, only the local lab's results will be used for this); all other subjects will attend clinic visits every 6 months beginning at 4 years of age until age 15.
    - Note: Subjects are not required to be positive for the same antibody at the next visit in order to be considered persistent autoantibody positive for the visit schedule after 4 years of age. For example the subject could be GAD positive at one visit and then MIAA positive at the next visit and be considered persistent autoantibody positive and the subject would be placed on the 3 month schedule.
- For subjects who become autoantibody positive at 4 years of age or older, the subject will be reinstated on the three month visit schedule at the first indication of autoantibody positivity and will stay on if persistent. If the next available sample is negative, thus the subject is not deemed persistent autoantibody positive, the subject will be seen every 6 months instead of every 3 months from that point on.
- Subjects who have been persistently single autoantibody positive, but who become negative to all antibodies for 1 calendar year or more will be placed on the biannual visit schedule after 4 years of age. Subjects who have been persistently multiple autoantibody positive, but who become negative to all antibodies for 1 year or more will remain on the three month visit schedule.

  The following provides specifications for the implementation:

  Before and leading up to the age of 4 years, if a child has been:

    - Persistent autoantibody positive before the age of 4 years and is still autoantibody positive he/she will remain on a three-month visit schedule after 4 years of age.

- Persistent single autoantibody positive before the age of 4 years, but has been autoantibody negative for 1 calendar year leading up to the age of 4 years, the subject will switch to the biannual schedule at 4 years of age.
- Persistent multiple autoantibody positive before the age of 4 years, but has been autoantibody negative for 1 year leading up to the age of 4 years, the subject will remain on the three month visit schedule at 4 years of age and beyond.

Children who become autoantibody positive at 4 years of age or older:

- Will go on the 3 month visit schedule at the first indication of autoantibody positivity. If the next available sample is negative, thus the subject is not deemed persistent autoantibody positive, the subject will be placed on the biannual visit schedule from that point on. If the subject is deemed persistent autoantibody positive the subject will follow a 3 month visit schedule from that point on.
- As above, a child with prior persistent single autoantibody positive status that has been negative for 1 calendar year (for all antibodies) will switch to the biannual visit schedule from that point on.
- As above, a child with prior persistent multiple autoantibody positive status that has been negative for 1 year (for all antibodies) will remain on the three month visit schedule.

- After the initial visit the visit window around subsequent visits is +/- 1.5 months around the month the visit is due (e.g. 6, 9, 12, 15, etc) up until 48 months of age. After 48 months of age if the child will follow the 3 month visit schedule the visit window around subsequent visits will continue to be +/- 1.5 months around the month the visit is due; if the child will follow the 6 month visit schedule the visit window around subsequent visits will be +/- 3 months around the month the visit is due. Table 9.1 outlines these windows.
- If visits in the schedule are missed, selected data or materials should be sent to parents for self administered completion or phone interviews should be attempted. These items are noted in table 9.1. If a subject has not been seen for a TEDDY visit for an extended amount of time and the site has not been able to collect the data from the missed appointments by mail or phone, as much data as possible should be collected at the next visit the subject attends.
    - These data elements must be collected within the window for the particular item (please see subject's participant's details page for specific windows for each item), for the center to be reimbursed for that data element according to the reimbursement schedule outlined in section 18 of the MOO.
    - Of particular importance are the 9-month Interview and Family History questionnaire that collect detailed demographic and autoimmune family history information related to the subject and family. Every effort should be made to collect this information even if the collection date is outside of the window (and therefore the site would not be reimbursed for the data element).

Table 9.1 TEDDY Visit Scheduling Windows and Missed Data Items to be collected if Visit not completed

Visit	Scheduling/Completion Window	Reimbursed Activity Y/N	Data Collection To Be Attempted if Visit Missed
3 month	3.0 - 4.5 months	Y	Must be completed to be enrolled in study
6 month	4.6 - 7.5 months	Y	6 mo Parent Questionnaires
		Y	TEDDY Book Extraction (best done as phone interview when visit is missed)
		N	Tracking form: Symptoms of Celiac Disease
		Y*	Stool Kits (recommend that parents always have at least 3-4 stool kits at home)
		N	Family History Questionnaire-send out for collection at 9 month visit.
		N	Water sample instructions for sample collection at 9 month visit
		Y	3 day diet record: collect if subject completed the record though missed the visit. Don't collect if record not completed.
9 month	7.6 – 10.5 months	Y	9 mo Primary Caretaker Interview (Demographic data is critical)
		Y	Collect Family History Questionnaire
		Y	TEDDY Book Extraction/Phone Interview
		Y	Collect Water Sample
		Y*	Stool Kits at home = 3
		Y	3-day diet record: same as in 6-month visit
12 month	10.6 – 13.5 months	Y	TEDDY Book Extraction/Phone Interview
		N	Tracking form: Symptoms of Celiac Disease
		Y*	Stool Kits at home=3
		Y	3-day diet record: same as in 6 month visit
15 month	13.6 – 16.5 months	Y	Annual Parent Questionnaire
		Y	TEDDY Book Extraction/Phone Interview
		Y*	Stool Kits at home=3
18 month	16.6 – 19.5 months	Y	TEDDY Book Extraction/Phone Interview
		N	Tracking form: Symptoms of Celiac Disease
		Y*	Stool Kits at home=3
		Y	3-day diet record: same as in 6-month visit
21 month	19.6 – 22.5 months	Y	TEDDY Book Extraction/Phone Interview
		Y	Update form for Primary Caretaker Interview
		Y*	Stool Kits at home=3
		N	Toenail sample pre-visit instructions for sample collection at 24 month visit
24 month	22.6 – 25.5 months	Y	TEDDY Book Extraction/Phone Interview
		N	Tracking form: Symptoms of Celiac Disease
		Y	Collect Toenail Sample

		Y* Y	Stool Kits at home=3 3-day diet record: same as in 6-month visit
27 month	25.6 – 28.5 months	Y Y Y*	TEDDY Book Extraction/Phone Interview Annual Parent Questionnaire Stool Kits at home =3
30 month	28.6 – 31.5 months	Y Y* Y	TEDDY Book Extraction/Phone Interview Stool Kits at home =3 3-day diet record: same as in 6-month visit
33 month	31.6 – 34.5 months	Y Y Y Y* N	TEDDY Book Extraction/Phone Interview Update form for Primary Caretaker Interview Update form for Family History Questionnaire Stool Kits at home =3 Water sample instructions for sample collection at 36 month visit
36 month	34.6 – 37.5 months	Y N Y Y* Y	TEDDY Book Extraction/Phone Interview Tracking form: Symptoms of Celiac Disease Collect Water Sample Stool Kits at home =3 3-day diet record: same as in 6-month visit
39 month	37.6 – 40.5 months	Y Y Y* N	TEDDY Book Extraction/Phone Interview Annual Parent Questionnaire Stool Kits at home =3 Salivary cortisol sample instructions for sample collection on the morning of the 42 month visit
42 month	40.6 – 43.5 months	Y Y* Y N	TEDDY Book Extraction/Phone Interview Stool Kits at home =3 3-day diet record: same as in 6-month visit Child Behavior Checklist
45 month	43.6 – 46.5 months	Y Y Y*	TEDDY Book Extraction/Phone Interview Update form for Primary Caretaker Interview Stool Kits at home =3 Toenail sample pre-visit instructions for sample collection at 48 month visit
48 month#	If child will follow 3 month visit schedule: 46.6 – 49.5 months If child will follow 6 month visit schedule: 46.6 – 51 months	Y Y N Y* Y	Annual Parent Questionnaire TEDDY Book Extraction/Phone Interview Tracking form: Symptoms of Celiac Disease Collect Toenail Sample Stool Kits at home =2 3-day diet record: same as in 6-month visit
51month#	49.6 – 52.5 months	Y	TEDDY Book Extraction/Phone Interview

54 month#	If child will follow 3 month visit schedule: 52.6 – 55.5 months If child will follow 6 month visit schedule: 51.1 - 57 months	Y Y Y Y* Y N N	TEDDY Book Extraction/Phone Interview Update form for Primary Caretaker Interview Update form for Family History Questionnaire Stool Kits at home =2 3-day diet record: same as in 6-month visit Child Behavior Checklist Water sample instructions for sample collection at 60 month visit
57 month#	55.6 – 58.5 months	Y N	TEDDY Book Extraction/Phone Interview Water sample instructions for sample collection at 60 month visit
5 year#	If child will follow 3 month visit schedule: 4 year 10.6 months – 5 year 1.5 months If child will follow 6 month visit schedule: 4 year 9.1 months – 5 year 3 months	Y Y N Y Y* Y	Annual Parent Questionnaire TEDDY Book Extraction/Phone Interview Tracking form: Symptoms of Celiac Disease Collect Water Sample Stool Kits at home =2 3-day diet record: same as in 6-month visit
5 year 3 month#	5 year 1.6 months – 5 year 4.5 months	Y	TEDDY Book Extraction/Phone Interview
5 year 6 month#	If child will follow 3 month visit schedule: 5 year 4.6 months – 5 year 7.5 months If child will follow 6 month visit schedule: 5 year 3.1 months – 5 year 9 months	Y Y* Y N	TEDDY Book Extraction/Phone Interview Stool Kits at home =2 3-day diet record: same as in 6-month visit Child Behavior Checklist Toenail sample pre-visit instructions for sample collection at 6 year visit
5 year 9 month#	5 year 7.6 months – 5 year 10.5 months	Y	TEDDY Book Extraction/Phone Interview Toenail sample pre-visit instructions for sample collection at 6 year visit
6 year#	If child will follow 3 month visit schedule: 5 year	Y Y N	Annual Parent Questionnaire TEDDY Book Extraction/Phone Interview Tracking form: Symptoms of Celiac Disease

	10.6 months – 6 year 1.5 months If child will follow 6 month visit schedule: 5 year 9.1 months – 6 year 3 months	Y Y*	Collect Toenail Sample Stool Kits at home =2 3-day diet record: same as in 6-month visit
6 year 3 month#	6 year 1.6 months – 6 year 4.5 months	Y	TEDDY Book Extraction/Phone Interview
6 year 6 month#	If child will follow 3 month visit schedule: 6 year 4.6 months – 6 year 7.5 months If child will follow 6 month visit schedule: 6 year 3.1 months – 6 year 9 months	Y Y Y* Y N N	TEDDY Book Extraction/Phone Interview Update form for Primary Caretaker Interview Stool Kits at home =2 3-day diet record: same as in 6-month visit Water sample instructions for sample collection at 7 year visit Toenail sample pre-visit instructions for sample collection at 7 year visit
6 year 9 month#	6 year 7.6 month – 6 year 10.5 month	Y N N	TEDDY Book Extraction/Phone Interview Water sample instructions for sample collection at 7 year visit Toenail sample pre-visit instructions for sample collection at 7 year visit
7 year#	If child will follow 3 month visit schedule: 6 year 10.6 months – 7 year 1.5 months If child will follow 6 month visit schedule: 6 year 9.1 months – 7 year 3 months	Y Y N Y Y Y* Y	Annual Parent Questionnaire TEDDY Book Extraction/Phone Interview Tracking form: Symptoms of Celiac Disease Collect Water Sample Collect Toenail Sample Stool Kits at home =2 3-day diet record: same as in 6-month visit
7 year 3 month#	7 year 1.6 months – 7 year 4.5 months	Y	TEDDY Book Extraction/Phone Interview

7 year 6 month#	If child will follow 3 month visit schedule: 7 year 4.6 months – 7 year 7.5 months If child will follow 6 month visit schedule: 7 year 3.1 months – 7 year 9 months	Y Y* Y N	TEDDY Book Extraction/Phone Interview Stool Kits at home =2 3-day diet record: same as in 6-month visit Toenail sample pre-visit instructions for sample collection at 8 year visit
7 year 9 month#	7 year 7.6 month – 7 year 10.5 month	Y N	TEDDY Book Extraction/Phone Interview Toenail sample pre-visit instructions for sample collection at 8 year visit
8 year#	If child will follow 3 month visit schedule: 7 year 10.6 months – 8 year 1.5 months If child will follow 6 month visit schedule: 7 year 9.1 months – 8 year 3 months	Y Y N N Y Y* Y	Annual Parent Questionnaire TEDDY Book Extraction/Phone Interview Tracking form: Symptoms of Celiac Disease Pubertal Status Assessment Form Collect Toenail Sample Stool Kits at home =2 *(Stool sample collections were stopped on all subjects in August 2018)* 3-day diet record: same as in 6-month visit
8 year 3 month#	8 year 1.6 months – 8 year 4.5 months	Y	TEDDY Book Extraction/Phone Interview
8 year 6 month#	If child will follow 3 month visit schedule: 8 year 4.6 months – 8 year 7.5 months If child will follow 6 month visit schedule: 8 year 3.1 months – 8 year 9 months	Y Y Y N Y* Y N N	TEDDY Book Extraction/Phone Interview Update form for Primary Caretaker Interview Update form for Family History Questionnaire Pubertal Status Assessment Form Stool Kits at home =2 *(Stool sample collections were stopped on all subjects in August 2018)* 3-day diet record: same as in 6-month visit Water sample instructions for sample collection at 9 year visit Toenail sample pre-visit instructions for sample collection at 9 year visit

8 year 9 month#	8 year 7.6 month – 8 year 10.5 month	Y N N	TEDDY Book Extraction/Phone Interview Water sample instructions for sample collection at 9 year visit Toenail sample pre-visit instructions for sample collection at 9 year visit
9 year#	If child will follow 3 month visit schedule: 8 year 10.6 months – 9 year 1.5 months If child will follow 6 month visit schedule: 8 year 9.1 months – 9 year 3 months	Y Y N N Y Y Y* Y	Annual Parent Questionnaire TEDDY Book Extraction/Phone Interview Tracking form: Symptoms of Celiac Disease Pubertal Status Assessment Form Collect Water Sample Collect Toenail Sample Stool Kits at home =2 *(Stool sample collections were stopped on all subjects in August 2018)* 3-day diet record: same as in 6-month visit
9 year 3 month#	9 year 1.6 months – 9 year 4.5 months	Y	TEDDY Book Extraction/Phone Interview
9 year 6 month#	If child will follow 3 month visit schedule: 9 year 4.6 months – 9 year 7.5 months If child will follow 6 month visit schedule: 9 year 3.1 months – 9 year 9 months	Y N Y* Y N	TEDDY Book Extraction/Phone Interview Pubertal Status Assessment Form Stool Kits at home =2 *(Stool sample collections were stopped on all subjects in August 2018)* 3-day diet record: same as in 6-month visit Toenail sample pre-visit instructions for sample collection at 10 year visit
9 year 9 month#	9 year 7.6 month – 9 year 10.5 month	Y N	TEDDY Book Extraction/Phone Interview Toenail sample pre-visit instructions for sample collection at 10 year visit
10 year#	If child will follow 3 month visit schedule: 9 year 10.6 months – 10 year 1.5 months If child will follow 6 month visit	Y Y N N Y Y*	Annual Parent Questionnaire TEDDY Book Extraction/Phone Interview Tracking form: Symptoms of Celiac Disease Pubertal Status Assessment Form Collect Toenail Sample Stool Kits at home =2 *(Stool sample collections were stopped on all subjects in August 2018)*

	schedule: 9 year 9.1 months – 10 year 3 months	Y	3-day diet record: same as in 6-month visit
10 year 3 month#	10 year 1.6 months – 10 year 4.5 months	Y	TEDDY Book Extraction/Phone Interview
10 year 6 month#	If child will follow 3 month visit schedule: 10 year 4.6 months – 10 year 7.5 months If child will follow 6 month visit schedule: 10 year 3.1 months – 10 year 9 months	Y Y N Y* Y N N	TEDDY Book Extraction/Phone Interview Update form for Primary Caretaker Interview Pubertal Status Assessment Form Stool Kits at home =2 *(Stool sample collections were stopped on all subjects in August 2018)* 3-day diet record: same as in 6-month visit *(Starting in August 2018 3-day diet records for the 10 year 6 month visit and on will only be collected from subjects who are persistent confirmed autoantibody positive)* Water sample instructions for sample collection at 11 year visit Toenail sample pre-visit instructions for sample collection at 11 year visit
10 year 9 month#	10 year 7.6 month – 10 year 10.5 month	Y N N	TEDDY Book Extraction/Phone Interview Water sample instructions for sample collection at 11 year visit Toenail sample pre-visit instructions for sample collection at 11 year visit
11 year#	If child will follow 3 month visit schedule: 10 year 10.6 months – 11 year 1.5 months If child will follow 6 month visit schedule: 10 year 9.1 months – 11 year 3 months	Y Y Y N N Y Y Y* Y	Annual Parent Questionnaire Annual Child Questionnaire TEDDY Book Extraction/Phone Interview Tracking form: Symptoms of Celiac Disease Pubertal Status Assessment Form Collect Water Sample Collect Toenail Sample Stool Kits at home =2 *(Stool sample collections were stopped on all subjects in August 2018)* 3-day diet record: same as in 6-month visit *(Starting in August 2018 3-day diet records for the 10 year 6 month visit and on will only be collected from subjects who are persistent confirmed autoantibody positive)*

11 year 3 month#	11 year 1.6 months – 11 year 4.5 months	Y	TEDDY Book Extraction/Phone Interview
11 year 6 month#	If child will follow 3 month visit schedule: 11 year 4.6 months – 11 year 7.5 months If child will follow 6 month visit schedule: 11 year 3.1 months – 11 year 9 months	Y N Y *(only 1 SDQ per visit reimbursed)* Y* Y N	TEDDY Book Extraction/Phone Interview Pubertal Status Assessment Form Parent SDQ Child SDQ Stool Kits at home =2 *(Stool sample collections were stopped on all subjects in August 2018)* 3-day diet record: same as in 6-month visit *(Starting in August 2018 3-day diet records for the 10 year 6 month visit and on will only be collected from subjects who are persistent confirmed autoantibody positive)* Toenail sample pre-visit instructions for sample collection at 12 year visit
11 year 9 month#	11 year 7.6 month – 11 year 10.5 month	Y N	TEDDY Book Extraction/Phone Interview Toenail sample pre-visit instructions for sample collection at 12 year visit
12 year#	If child will follow 3 month visit schedule: 11 year 10.6 months – 12 year 1.5 months If child will follow 6 month visit schedule: 11 year 9.1 months – 12 year 3 months	Y Y Y N N Y Y* Y	Annual Parent Questionnaire Annual Child Questionnaire TEDDY Book Extraction/Phone Interview Tracking form: Symptoms of Celiac Disease Pubertal Status Assessment Form Collect Toenail Sample Stool Kits at home =2 *(Stool sample collections were stopped on all subjects in August 2018)* 3-day diet record: same as in 6-month visit *(Starting in August 2018 3-day diet records for the 10 year 6 month visit and on will only be collected from subjects who are persistent confirmed autoantibody positive)*
12 year 3 month#	12 year 1.6 months – 12 year 4.5 months	Y	TEDDY Book Extraction/Phone Interview
12 year 6 month#	If child will follow 3 month visit schedule: 12 year	Y Y Y	TEDDY Book Extraction/Phone Interview Update form for Primary Caretaker Interview Update form for Family History Questionnaire

	4.6 months – 12 year 7.5 months If child will follow 6 month visit schedule: 12 year 3.1 months – 12 year 9 months	N Y* Y N	Pubertal Status Assessment Form Stool Kits at home =2 *(Stool sample collections were stopped on all subjects in August 2018)* 3-day diet record: same as in 6-month visit *(Starting in August 2018 3-day diet records for the 10 year 6 month visit and on will only be collected from subjects who are persistent confirmed autoantibody positive)* Water sample instructions for sample collection at 13 year visit Toenail sample pre-visit instructions for sample collection at 13 year visit
12 year 9 month#	12 year 7.6 month – 12 year 10.5 month	Y N	TEDDY Book Extraction/Phone Interview Water sample instructions for sample collection at 13 year visit Toenail sample pre-visit instructions for sample collection at 13 year visit
13 year#	If child will follow 3 month visit schedule: 12 year 10.6 months – 13 year 1.5 months If child will follow 6 month visit schedule: 12 year 9.1 months – 13 year 3 months	Y Y Y N N Y Y Y* Y	Annual Parent Questionnaire Annual Child Questionnaire TEDDY Book Extraction/Phone Interview Tracking form: Symptoms of Celiac Disease Pubertal Status Assessment Form Collect Water Sample Collect Toenail Sample Stool Kits at home =2 *(Stool sample collections were stopped on all subjects in August 2018)* 3-day diet record: same as in 6-month visit *(Starting in August 2018 3-day diet records for the 10 year 6 month visit and on will only be collected from subjects who are persistent confirmed autoantibody positive)*
13 year 3 month#	13 year 1.6 months – 13 year 4.5 months	Y	TEDDY Book Extraction/Phone Interview
13 year 6 month#	If child will follow 3 month visit schedule: 13 year 4.6 months – 13 year 7.5 months If child will follow 6 month visit	Y N Y *(only 1 SDQ per visit reimbursed)* Y*	TEDDY Book Extraction/Phone Interview Pubertal Status Assessment Form Parent SDQ Child SDQ

	schedule: 13 year 3.1 months – 13 year 9 months	Y N	Stool Kits at home =2 *(Stool sample collections were stopped on all subjects in August 2018)* 3-day diet record: same as in 6-month visit *(Starting in August 2018 3-day diet records for the 10 year 6 month visit and on will only be collected from subjects who are persistent confirmed autoantibody positive)* Toenail sample pre-visit instructions for sample collection at 14 year visit
13 year 9 month#	13 year 7.6 month – 13 year 10.5 month	Y N	TEDDY Book Extraction/Phone Interview Toenail sample pre-visit instructions for sample collection at 14 year visit
14 year#	If child will follow 3 month visit schedule: 13 year 10.6 months – 14 year 1.5 months If child will follow 6 month visit schedule: 13 year 9.1 months – 14 year 3 months	Y Y Y N N Y Y* Y	Annual Parent Questionnaire Annual Child Questionnaire TEDDY Book Extraction/Phone Interview Tracking form: Symptoms of Celiac Disease Pubertal Status Assessment Form Collect Toenail Sample Stool Kits at home =2 *(Stool sample collections were stopped on all subjects in August 2018)* 3-day diet record: same as in 6-month visit *(Starting in August 2018 3-day diet records for the 10 year 6 month visit and on will only be collected from subjects who are persistent confirmed autoantibody positive)*
14 year 3 month#	14 year 1.6 months – 14 year 4.5 months	Y	TEDDY Book Extraction/Phone Interview
14 year 6 month#	If child will follow 3 month visit schedule: 14 year 4.6 months – 14 year 7.5 months If child will follow 6 month visit schedule: 14 year 3.1 months – 14 year 9 months	Y Y N Y* Y N	TEDDY Book Extraction/Phone Interview Update form for Primary Caretaker Interview Pubertal Status Assessment Form Stool Kits at home =2 *(Stool sample collections were stopped on all subjects in August 2018)* 3-day diet record: same as in 6-month visit *(Starting in August 2018 3-day diet records for the 10 year 6 month visit and on will only be collected from subjects who are persistent confirmed autoantibody positive)* Toenail sample pre-visit instructions for sample collection at 15 year visit

14 year 9 month#	14 year 7.6 month – 14 year 10.5 month	Y N	TEDDY Book Extraction/Phone Interview Toenail sample pre-visit instructions for sample collection at 15 year visit
15 year#	If child will follow 3 month visit schedule: 14 year 10.6 months – 15 year 1.5 months If child will follow 6 month visit schedule: 14 year 9.1 months – 15 year 3 months	Y Y Y N N Y Y* Y	End of TEDDY Parent Questionnaire End of TEDDY Child Questionnaire TEDDY Book Extraction/Phone Interview Tracking form: Symptoms of Celiac Disease Pubertal Status Assessment Form Collect Toenail Sample Stool Kits at home =2 *(Stool sample collections were stopped on all subjects in August 2018)* 3-day diet record: same as in 6-month visit *(Starting in August 2018 3-day diet records for the 10 year 6 month visit and on will only be collected from subjects who are persistent confirmed autoantibody positive)*

Y* = reimbursed for stool samples received by Repository, not for kits given out.

= Children four years of age and older who have been deemed persistent autoantibody positive will remain on the 3 month visit schedule (confirmation results from the confirmatory Autoantibody lab will not be taken into consideration for determining the subject's visit schedule, only the local lab's results will be used for this); all other subjects will attend clinic visits every 6 months beginning at 4 years of age until age 15. For subjects who become autoantibody positive at 4 years of age or older, the subject will be reinstated on the three month visit schedule at the first indication of autoantibody positivity and will stay on if persistent. If the next available sample is negative, thus the subject is not deemed persistent autoantibody positive, the subject will be seen every six months instead of every three months from that point on. Subjects who have been persistently single autoantibody positive, but who become negative to all antibodies for 1 year or more will be placed on the biannual visit schedule after 4 years of age. Subjects who have been persistently multiple autoantibody positive, but who become negative to all antibodies for 1 year will remain on the three month visit schedule.

Table 9.2 Visit Schedule and Summary of Contents

	Age in Months																						
	Screening		Follow-Up																				
Sampling Frequency	**Birth**	**<4**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**15**	**18**	**21**	**24**	**27**	**12-48 mo Monthly Test**	**24-48 mo Every 3 mo Tests**	**24-48 mo Every 6 mo Tests**	**>48 mo Every 3 mo Tests**	**>48 mo Every 6 mo Tests**	**>48 mo Annual Tests**
			Inform Parents of child's HLA risk	Mail initial enrollment and questionnaire packet																					
Blood**	**X***	**X***			**X+**			**X+**			**X+**			**X+**	**X+**	**X+**	**X+**	**X+**	**X+**		**X+#**			**X+#**	
Stool					**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X(until 10 years)**	**X(at 10 years); Collection stopped August 2018**	
Tap Water											**X**									**Collected every 2 years beginning at the 36 month visit**					
Toenail Clippings																		**X**			**Collected every 2 years beginning at the 24 month visit; Starting May 2017 collected every 1 year**				
Salivary Cortisol***																				**Collected when child is 3.5, 4.5 and 5.5 years of age**					
Nasal Swab											**X**			**X**	**X**	**X**	**X**	**X**	**X**		**X#**			**X#**	
Urine																						**X (begins at 3 years)**		**X**	
Primary Tooth	**Collect when tooth naturally falls out - ages will vary**																								
Weight and Length/Height Measurements; Body composition on some subjects					**X**			**X**			**X**			**X**	**X**	**X**	**X**	**X**	**X**		**X#**			**X#**	
Diet Questionnaires																									
-maternal pregnancy diet				**X**																					
-3 day diet record					**X**			**X**			**X**			**X**		**X**		**X**				**X**		**X^**	
Environmental Exposure Questionnaires																									
-maternal pregnancy/birth questionnaire				**X**																					
- parent questionnaire				**X**				**X**							**X**				**X**				**Annually after 27 mos**		
- child questionnaire																									**X(begins at 10 years)**
Demographic/Family History/Other questionnaire											**X**									**Demographic data will be updated every 2 years thereafter; Family History data will be updated every 4 years thereafter**					
TEDDY Book Extraction					**X**			**X**			**X**			**X**	**X**	**X**	**X**	**X**	**X**		**X#**			**X#**	
Child Behavior Checklist/ Strengths and Difficulties Questionnaire																				**CBCL completed when child is 3.5, 4.5 and 5.5 years of age; SDQ completed by both parent and child when child is 11.5 and 13.5 years of age**					

Physical Activity Assessment																								**X (begins at 5 years) %**
Pubertal Status Assessment																							**X (begins at 8 years)**	

***If cord blood is not available at birth for HLA typing then capillary blood should be drawn.**
+ If venous blood is not available at every three month office visit, then capillary blood should be taken.
**** A blood sample will be obtained by the 24 month visit from mothers who have type 1 or 2 diabetes or gestational diabetes as well as from a mother whose child is shown to be autoantibody positive at three or six months of age. An optional venous blood draw of the mother is obtained at 12-14 weeks of pregnancy, and at the birth of the baby.**
*****Each TEDDY Clinical Center will decide whether or not their site will participate in the Salivary Cortisol Sub-Study**
#Children four years of age and older who have been deemed persistent autoantibody positive will remain on the three month visit schedule; this sample/form will be collected/completed at these visits.
^ Continue to collect 3 day diet records every 6 months from subjects who are single or multiple persistent confirmed autoantibody positive (even if the subject reverts to autoantibody negativity), stop 3 day diet record collections on all other subjects after the 10 year visit. Should a subject be deemed single or multiple persistent confirmed autoantibody positive after the 10 year visit, the 3 day diet record collection will be restarted at the next visit.
% Continue to collect physical activity assessments annually from subjects who are single or multiple persistent confirmed autoantibody positive (even if the subject reverts to autoantibody negativity), stop physical activity assessments on all other subjects after the 10 year visit. Should a subject be deemed single or multiple persistent confirmed autoantibody positive after the 10 year visit, the physical activity assessment will be restarted at the next visit.

9.2 Clinic Visit Data

9.2.1 Interviews/Questionnaires-See Sections 10, 11, 12

The study nurse or equivalent will conduct interviews with the child's mother or primary caretaker at each clinical visit when the child is 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45 and 48 months of age. At 4 years of age and beyond those children who have been deemed persistent autoantibody positive will follow a 3 month interview schedule (confirmation results from the confirmatory Autoantibody lab will not be taken into consideration for determining the subject's visit schedule, only the local lab's results will be used for this); interviews for all other subjects will be conducted on a biannual basis beginning at 4 years of age. (For subjects who become autoantibody positive at 4 years of age or older, the subject will be reinstated on the three month visit schedule at the first indication of autoantibody positivity and will stay on if persistent. If the next available sample is negative, thus the subject is not deemed persistent autoantibody positive, the subject will be seen every six months instead of every three months from that point on. Subjects who have been persistently autoantibody positive, but who become negative to all antibodies for 1 year or more will be placed on the biannual visit schedule after 4 years of age.) See MOO Section 10, 11 and 12 for details of most interviews and questionnaires except as noted below.

Demographic and Family History of Autoimmune Disease and Diabetes

Abbreviated demographic, family history and tracking information is gathered on the screening form and at the first visit at the age of 3 months. As the study earns the families trust and confidence more comprehensive demographic information will be gathered through the 9 month visit interview. A detailed family history questionnaire will be given out at the 6-month visit and will be reviewed at the 9 month visit. This family history questionnaire focuses specifically on family history of autoimmune diseases and diabetes for first and second degree biologically related relatives. The demographic data will be updated with the family every 2 years thereafter and the family history data will be updated with the family every 4 years thereafter.

Relevant Forms: Screening, 3-m Interview, Family History, 9-m Interview, Update form for primary caretaker interview, Update form for family history questionnaire

Medical

Medical information will be obtained by interview or questionnaire at each clinic visit when the child is 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45 and 48 months of age. At 4 years of age and beyond medical information will be collected every 3 months on those children who have been deemed persistent autoantibody positive (confirmation results from the confirmatory Autoantibody lab will not be taken into consideration for determining the subject's visit schedule, only the local lab's results will be used for this); medical information on all other subjects will be collected on a biannual basis beginning at 4 years of age. (For subjects who become autoantibody positive at 4 years of age or older,

the subject will be reinstated on the three month visit schedule at the first indication of autoantibody positivity and will stay on if persistent. If the next available sample is negative, thus the subject is not deemed persistent autoantibody positive, the subject will be seen every six months instead of every three months. Subjects who have been persistently autoantibody positive, but who become negative to all antibodies for 1 year or more will be placed on the biannual visit schedule after 4 years of age.) In addition, the parents will be asked to consent to allow TEDDY personnel to access the child's medical record in the event that the child has been hospitalized, or has/had any outpatient treatments.

Relevant Forms: First TEDDY Questionnaire, 3-m Interview, 6-m Questionnaire, TEDDY Book Extraction, Annual Questionnaire.

Maternal Nutrition

Measurement of maternal diet will be collected by means of a short food frequency questionnaire (FFQ), which concentrates on the intakes of fish and fish products, milk and milk products, and cereal and cereal products during the eighth month of pregnancy (for Finland and Germany) or during the ninth month for the United States and Sweden. The use of dietary supplements is asked as well as source of drinking water. The height of the mother is inquired as well as the weight before pregnancy and the weight gain during pregnancy. This questionnaire will be mailed home to the mother prior to the first clinic visit.

Relevant Forms: First Mother Questionnaire

Dietary Intake of the Child

In addition to food consumption, dietary habits of the participating infants (e.g. feeding pattern) will be assessed by a structured interview at each clinic visit, and records kept by the mother in the TEDDY Book. The duration of total and exclusive breastfeeding, age at introduction of various foods during the first 2 years of life, type of infant formulas used, source of drinking water (local waterworks, bottled water, private wells), elimination diets, and use of dietary supplements will be recorded.

Primary caretakers (usually mothers) will be trained during the three-month clinic visit to keep 3-day food diaries of the child's dietary intake at 3 month intervals during the first year of life and biannually thereafter. In August 2018, the collection protocol was changed so as to continue to collect 3 day diet records every 6 months from subjects who are single or multiple persistent confirmed autoantibody positive (even if the subject reverts to autoantibody negativity) and to stop 3 day diet record collections on all other subjects after the 10 year visit. Should a subject be deemed single or multiple persistent confirmed autoantibody positive after the 10 year visit, the 3 day diet record collection will be restarted at the next visit. A 24-hour recall of the child's diet will be obtained at the first (3-month) visit. At each clinic visit, the diet records will be reviewed by trained study personnel with the primary caretaker. See MOO Section 12 for detailed protocol.

Infectious Illnesses/Immunizations of the Child

At each clinic visit when the child is 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45 and 48 months of age, information on infectious illnesses and immunizations that occurred since birth or the last visit will be recorded. At 4 years of age and beyond information on infectious illnesses and immunizations will be collected every 3 months from those children who have been deemed persistent autoantibody positive confirmation results from the confirmatory Autoantibody lab will not be taken into consideration for determining the subject's visit schedule, only the local lab's results will be used for this); information on infectious illnesses and immunizations will be collected from all other subjects on a biannual basis beginning at 4 years of age. (For subjects who become autoantibody positive at 4 years of age or older, the subject will be reinstated on the three month visit schedule at the first indication of autoantibody positivity and will stay on if persistent. If the next available sample is negative, thus the subject is not deemed persistent autoantibody positive, the subject will be seen every six months instead of every three months from that point on. Subjects who have been persistently autoantibody positive, but who become negative to all antibodies for 1 year or more will be placed on the biannual visit schedule after 4 years of age.) At 3 months, this will be done by a standardized interview. At subsequent visits, this will be done by extracting the information from the TEDDY Book. See MOO Sections 10 and 11 for detailed protocol.

Psychosocial

The psychosocial areas of investigation include questions about life events in the parents and child's life, perceived diabetes risk, anxiety about the child's health, comfort with the study and post-partum depression. Some questions are asked of both parents in the first questionnaire that is mailed and reviewed at the first visit, others questions are completed by self-administered questionnaires at the 6, 15, 27, 39, 48 month study visits, and annually thereafter through the 14 year visit. The Annual Child Questionnaire administration will begin at age 10 and will be administered yearly thereafter through the 14 year visit. At the 15 year visit an End of TEDDY Parent Questionnaire and an End of TEDDY Child Questionnaire will be administered since it will be the last TEDDY study visit. The administration of the Child Life Events list will be very similar to the parent-completed Life Events list and will be given at every visit beginning at age 10 (i.e., twice a year for autoantibody negative families, four times a year for children who have been deemed persistent autoantibody positive).

The Child Behavior Checklist (CBCL) will also be administered in the TEDDY study. It is a well-validated instrument originally developed by Dr. Thomas Achenbach that has been used extensively worldwide for over 25 years. It is a measure of internalizing behavior (affective and anxiety problems) and externalizing behaviors (attention deficit/hyperactivity problems and oppositional defiant problems) and will be completed by one of the child's parents when the child is 3.5, 4.5 and 5.5 years of age.

As children age, it will be important to gather self-report data on their psychological functioning. Given the lengthy nature of the CBCL, TEDDY will move from the CBCL

(parent-report only) to the Strengths and Difficulties Questionnaire (SDQ) (parent- and child-report) at 11.5 and 13.5 years of age. The SDQ is a well-validated screening instrument used in the US National Children's Study as well as internationally in TEDDY countries that assesses child psychological functioning across five behavioral and emotional domains. The SDQ has 25-items and will allow a determination of whether TEDDY children are comparable to children from the general population in terms of their psychological and behavioral functioning. The SDQ has been cross-validated with the CBCL, thus past TEDDY data using the CBCL can be easily compared.

9.2.2 Clinical Measurements -See Section 13

Weight and length/height measurements will be taken at each clinic visit. Weight will be measured in grams (g). Children old enough to stand on a scale will be measured in light clothing on a scale. Length/height will be measured in centimeters (cm). Length will be measured on all children up to two years of age. After the child is 2 years old the standing height will be measured with the child standing barefoot.

Starting in May 2017, in addition to height and weight, body fat will also be measured on some subjects. Fat distribution may be important in the development of type 1 diabetes (T1D). There is evidence that increased height and/or weight gain may have a role in the etiology of T1D, but no information is available whether the amount or distribution of body fat could play a role in the etiology of T1D. Availability of body fat measurement will increase the usability of the rich data on dietary, psychosocial and other covariates of obesity that is being collected in TEDDY. By measuring body fat in TEDDY, we can better analyze factors related to being overweight or obese. Body composition (weight and kilograms of body fat) will be measured at every TEDDY visit (on some subjects) using the TANITA® DC-430U Dual Frequency Total Body Composition Analyzer. The data will be recorded on the TEDDY Physical Exam Form by the Clinical Centers.

9.2.3 Medical record review

The medical record of the child will be accessed following parental consent to extract specific medical information in the event that the child has been hospitalized, or has any outpatient treatments. The information will be entered in the database.

9.2.4 Blood, Stool and Other Specimen Collection-See Sections 13, 14 and 15 for details

To the extent possible, blood and stool samples will be collected, processed, and stored in such a manner as to be compatible with both immediate and future testing requirements (in August 2018 all stool sample collections were stopped on all subjects). In general, most specimens will be stored at – 70°C. Since future testing may include new analyses and technologies, it may not be possible to prepare for all possibilities.

At the earlier visits, total volume of blood collected at each visit ranges from 6.5 to 25.5 mls per visit, however as children get older additional blood volume will be collected based upon local IRB/Ethics Board approval and the weight of the child. At no time will the blood draw volume exceed what is allowable according to the subject's body weight - 3 mL/kg per visit. Blood will be processed for serum, plasma, whole blood, peripheral blood mononuclear cells (PBMC) and RNA. Unique vial barcode numbers will be etched onto cryovials. Aliquots will be mailed in batches on dry ice from the clinical centers to the reference laboratories. Additional aliquots will be sent in batches to the NIDDK repository.

Monthly stool samples will be collected by the parents up until 48 months of age; after 48 months of age stool samples will be collected every 3 months until 10 years of age and then every 6 months thereafter (in August 2018 all stool sample collections were stopped on all subjects). In the US parents will ship the stool samples directly to the NIDDK repository. At the European sites parents will send samples to the clinical centers and these will be batched and sent frozen to the NIDDK repository by the clinical center. Parents will be instructed in this procedure at the 3-month visit and stool sample kits and mailers (3) will be given to the parents at each visit thereafter.

Tap water samples will be collected every 2 years starting at 3 years of age. Toenail clippings will be collected every 1 year starting at 2 years of age. Salivary cortisol samples will be collected when the child is 3.5 years, 4.5 years and 5.5 years of age. Nasal swab samples will begin being collected every 3 months when the child is 9 months of age; at 4 years of age and beyond nasal swab samples will be collected every 3 months from those children who have been deemed persistent autoantibody positive and from all other subjects on a biannual basis. Urine samples will be collected every 6 months beginning at 3 years of age. Primary tooth samples will be collected when the tooth naturally falls out, ages of children will vary.

9.3 Clinic Visits Description Summary

Enrollment Packet

An enrollment packet will be sent to the child's family after the initial telephone call or face-to-face meeting where the HLA results were explained. The enrollment packet will include material on the study for them to review. A time for further discussion about enrolling in the follow-up portion of the study will be arranged. The enrollment packet should include the following:

- HLA screening results letter
- Follow-up Study Brochure that includes a frequently asked questions section
- Information outlining what's required for each visit-What to Expect Document (which can be found in the MOO 7 Appendix)
- Site Specific Options: Other information for diabetes education

Mailed Questionnaire Packet

About 2 weeks before the child's first visit a reminder about the visit and the items listed below will be mailed home to the family. A reminder call is recommended the day before the visit. If the TEDDY child is being cared for by someone other than the mother or father the First Questionnaire Primary Caretaker should be sent instead of the First questionnaires for Mother and Father. If the father is the only parent present then he is sent the primary caretaker interview only. The contents of the mailed questionnaire packet should include:

- First Questionnaire Mother
- First Questionnaire Father
- First Questionnaire Primary Caretaker – only if needed
- What to Expect Document if not previously sent (which can be found in the MOO 7 Appendix), recommend not sending Follow-up Informed Consents home
- Map and directions to the clinic
- Parking pass – if needed

3 Month Visit-

A parent or legal guardian must attend the first visit and sign the informed consent for child to be enrolled. Expected length of this visit is 1.5 to 2.0 hours.

The TEDDY diabetes informational card (see Appendix A) is to be given to all enrolled families in the TEDDY study – this requirement was added in May 2009, so for new subjects since then the card should be given to the family by the 6 month visit and for those subjects enrolled before this was added the card should be given at the next scheduled TEDDY visit.

Forms:

Follow-Up Informed Consent, HIPAA Authorizations (US Sites only)
Enrollment Form (online form found on the TEDDY website)
Review of First Questionnaire Mother
Review of First Questionnaire Father
Review of First Questionnaire Primary Caretaker – only if needed
3 Month Interview
Physical Exam Form and Sample Collection Checklist
24 Hour Recall
TEDDY Contact Information Update Form-for local clinic use only

Procedures:

Length
Weight
Blood Draw from Child (total recommended volume 6.5 ml):

Serum:	Autoantibodies
	Serum Cytokines/Inflammation markers
Plasma:	Enterovirus and Rotavirus PCR

Enterovirus and Rotavirus antibodies
Additional Infectious Agents
Vitamin D
Red blood cell membrane fatty acid
Buffy Coat (or PBMC from selected subjects)
RNA
Maternal AA sample if mother has type 1 or 2 diabetes or gestational diabetes (at 6 month visit - and/or child is shown to be autoantibody positive at 3 months of age; at 9 month visit and/or child is shown to be autoantibody positive at 3 or 6 months of age) – this sample is only collected from the mother one time during the study and can be collected up to the 24 month visit

In case the optimal proposed blood volume is not available, particularly at the earliest time points, the priorities for blood samples are as follows:

1.	serum	0.1-0.5 mL whole blood volume
2.	plasma, RBC, PBMC	0.6-1.0 mL whole blood volume
3.	mRNA	2.5 mL whole blood volume
4.	Any additional storage	

If mother has T1, T2, or GDM, blood will be drawn to test for autoantibodies at the 3, 6 or 9 month visit regardless of child's antibody status. If child tests positive at the 3 or 6 month visit a maternal sample should be requested regardless of diabetes status in the mother. Maternal informed consent for this test can be done as a separate consent or it can be included in the main follow-up informed consent document. This may vary by local IRB requirements.

Instructions for parent:
Stool sample collection kits (for monthly sample collection at home)
3 day diet records
TEDDY Book

6 Month Visit

Forms:
1-2 6 Month Questionnaires (Mother and Father, or primary caretaker)
Physical Exam Form
3 Day Diet Record
TEDDY Book Extraction
Tracking form: Symptoms of Celiac Disease

Procedures:
Length
Weight
Blood Draw (total recommended volume 8.5 ml):
Serum:

Autoantibodies
Serum Cytokines/Inflammation markers

Plasma:
Enterovirus and Rotavirus PCR
Enterovirus and Rotavirus antibodies
Additional Infectious Agents
Vitamin D
Alpha-tocopherol, Gamma-tocopherol
Carotenoids
Ascorbic Acid

Red blood cell membrane fatty acid
Buffy Coat (or PBMC from selected subjects)
RNA
Maternal AA sample if mother has type 1 or 2 diabetes or gestational diabetes and/or child is shown to be autoantibody positive at 3 months of age (at 9 month visit and/or child is shown to be autoantibody positive at 3 or 6 months of age) – this sample is only collected from the mother one time during the study and can be collected up to the 24 month visit

In case the optimal proposed blood volume is not available, particularly at the earliest time points, the priorities for blood samples are as follows:

1.	serum	0.1-0.5 mL whole blood volume
2.	plasma, RBC, PBMC	0.6-1.0 mL whole blood volume
3.	mRNA	2.5 mL whole blood volume
4.	Any additional storage	

Instructions/Materials for parent:
Stool sample collection kits (for monthly sample collection at home)
3 day diet record instructions
Tap Water Sample instructions and supplies (for collection at home; sample should be brought to 9 month visit)
Family History Questionnaire

9 Month Visit

Forms:
9 Month Interview
Family History Questionnaire-reviewed
Physical Exam Form
3 Day Diet Record
TEDDY Book Extraction

Procedures:
Length

Weight
Blood Draw (total recommended volume 11.5 ml (this includes 1 ml for HLA confirmation sample)):
- Serum:
  - Autoantibodies
  - Serum Cytokines/Inflammation markers
- Plasma:
  - Enterovirus and Rotavirus PCR
  - Enterovirus and Rotavirus antibodies
  - Additional Infectious Agents
  - Vitamin D
- Buffy Coat (or PBMC from selected subjects)
- RNA
- HLA confirmation sample - a whole blood sample will be drawn from subjects at the 6, 9 12 or 15 month clinic visit for better definition and additional genotyping. Sites are encouraged to complete this collection by the earliest visit with a full volume blood draw, but in all cases by the 15 month visit. If the HLA confirmation sample is collected at the 6 month visit, only 0.5 mL of blood is required to be collected for this sample. If the HLA confirmation sample is collected at the 9, 12 or 15 month visit 1 mL of blood should be collected for this sample.
- Maternal AA sample if mother has type 1 or 2 diabetes or gestational diabetes and/or child is shown to be autoantibody positive at 3 or 6 months of age – this sample is only collected from the mother <u>one</u> time during the study and can be collected up to the 24 month visit

Nasal Swab
Collect Water Sample brought from home

In case the optimal proposed blood volume is not available, particularly at the earliest time points, the priorities for blood samples are as follows:

1.	serum	0.1-0.5 mL whole blood volume
2.	plasma, RBC, PBMC	0.6-1.0 mL whole blood volume
3.	mRNA	2.5 mL whole blood volume
4.	Any additional storage	

<u>Instructions/Materials for parent:</u>
Stool sample collection kits (for monthly sample collection at home)
3 day diet record instruction

12 Month Visit

<u>Forms:</u>
Physical Exam Form
3 Day Diet Record
TEDDY Book Extraction

Tracking form: Symptoms of Celiac Disease

Procedures:
Length
Weight
Blood Draw (total recommended volume 16.5 ml):
- Serum:
  - Autoantibodies
  - Serum Cytokines/Inflammation markers
- Plasma:
  - Enterovirus and Rotavirus PCR
  - Enterovirus and Rotavirus antibodies
  - Additional Infectious Agents
  - Vitamin D
  - Alpha-tocopherol, Gamma-tocopherol
  - Carotenoids
  - Ascorbic Acid
- Red blood cell membrane fatty acid
- Buffy Coat (or PBMC from selected subjects)
- RNA
- HbA1c sample if subject meets the following criteria: An HbA1c sample will be drawn at the next TEDDY visit and every visit thereafter from children who are positive at the 9 month visit or later for at least one autoantibody (regardless of autoantibody positivity confirmation or persistence).
- Maternal AA sample if mother has type 1 or 2 diabetes or gestational diabetes and/or child is shown to be autoantibody positive at 3 or 6 months of age – this sample is only collected from the mother one time during the study and can be collected up to the 24 month visit

Nasal Swab

In case the optimal proposed blood volume is not available, particularly at the earliest time points, the priorities for blood samples are as follows:

1.	serum	0.1-0.5 mL whole blood volume
2.	plasma, RBC, PBMC	0.6-1.0 mL whole blood volume
3.	mRNA	2.5 mL whole blood volume
4.	Any additional storage	

Instructions/Materials for parent:
Stool sample collection kits (for monthly sample collection at home)

15 Month Visit

Forms:

Annual Questionnaire
Physical Exam Form
TEDDY Book Extraction

Procedures:
Length
Weight
Blood Draw (total recommended volume 16.5 ml):
- Serum:
  - Autoantibodies
  - Serum Cytokines/Inflammation markers
- Plasma:
  - Enterovirus and Rotavirus PCR
  - Enterovirus and Rotavirus antibodies
  - Additional Infectious Agents
- Buffy Coat (or PBMC from selected subjects)
- RNA
- HbA1c sample if subject meets the following criteria: An HbA1c sample will be drawn at the next TEDDY visit and every visit thereafter from children who are positive at the 9 month visit or later for at least one autoantibody (regardless of autoantibody positivity confirmation or persistence).
- Maternal AA sample if mother has type 1 or 2 diabetes or gestational diabetes and/or child is shown to be autoantibody positive at 3 or 6 months of age – this sample is only collected from the mother one time during the study and can be collected up to the 24 month visit

Nasal Swab

In case the optimal proposed blood volume is not available, particularly at the earliest time points, the priorities for blood samples are as follows:

1.	serum	0.1-0.5 mL whole blood volume
2.	plasma, RBC, PBMC	0.6-1.0 mL whole blood volume
3.	mRNA	2.5 mL whole blood volume
4.	Any additional storage	

Instructions/Materials for parent:
Stool sample collection kits (for monthly sample collection at home)
3 day diet record instruction

18 Month Visit

Forms:
Physical Exam Form
3 Day Diet Record
TEDDY Book Extraction

Tracking form: Symptoms of Celiac Disease

Procedures:
Length
Weight
Blood Draw (total recommended volume 16.5 ml):
- Serum:
  - Autoantibodies
  - Serum Cytokines/Inflammation markers
- Plasma:
  - Enterovirus and Rotavirus PCR
  - Enterovirus and Rotavirus antibodies
  - Additional Infectious Agents
- Buffy Coat (or PBMC from selected subjects)
- RNA
- HbA1c sample if subject meets the following criteria: An HbA1c sample will be drawn at the next TEDDY visit and every visit thereafter from children who are positive at the 9 month visit or later for at least one autoantibody (regardless of autoantibody positivity confirmation or persistence).
- Maternal AA sample if mother has type 1 or 2 diabetes or gestational diabetes and/or child is shown to be autoantibody positive at 3 or 6 months of age – this sample is only collected from the mother one time during the study and can be collected up to the 24 month visit

Nasal Swab

In case the optimal proposed blood volume is not available, particularly at the earliest time points, the priorities for blood samples are as follows:

1.	serum	0.1-0.5 mL whole blood volume
2.	plasma, RBC, PBMC	0.6-1.0 mL whole blood volume
3.	mRNA	2.5 mL whole blood volume
4.	Any additional storage	

Instructions/Materials for parent:
Stool sample collection kits (for monthly sample collection at home)

21 Month Visit

Forms:
Physical Exam Form
TEDDY Book Extraction
Update form for Primary Caretaker

Procedures:
Length

Weight
Blood Draw (total recommended volume 20.5 ml):
- Serum:
  - Autoantibodies
  - Serum Cytokines/Inflammation markers
- Plasma:
  - Enterovirus and Rotavirus PCR
  - Enterovirus and Rotavirus antibodies
  - Additional Infectious Agents
- Buffy Coat (or PBMC from selected subjects)
- RNA
- HbA1c sample if subject meets the following criteria: An HbA1c sample will be drawn at the next TEDDY visit and every visit thereafter from children who are positive at the 9 month visit or later for at least one autoantibody (regardless of autoantibody positivity confirmation or persistence).
- Maternal AA sample if mother has type 1 or 2 diabetes or gestational diabetes and/or child is shown to be autoantibody positive at 3 or 6 months of age – this sample is only collected from the mother one time during the study and can be collected up to the 24 month visit

Nasal Swab
In case the optimal proposed blood volume is not available, particularly at the earliest time points, the priorities for blood samples are as follows:

1.	serum	0.1-0.5 mL whole blood volume
2.	plasma, RBC, PBMC	0.6-1.0 mL whole blood volume
3.	mRNA	2.5 mL whole blood volume
4.	Any additional storage	

Instructions/Materials for parent:
Stool sample collection kits (for monthly sample collection at home)
3 day diet record instruction
Toenail clipping pre-visit instructions

24 Month Visit

Forms:
Physical Exam Form
3 Day Diet Record
TEDDY Book Extraction
Tracking form: Symptoms of Celiac Disease

Procedures:
Height
Weight

Blood Draw (total recommended volume 20.5 ml):
- Serum:
  - Autoantibodies
  - Serum Cytokines/Inflammation markers
  - Transglutaminase Antibodies
- Plasma:
  - Enterovirus and Rotavirus PCR
  - Enterovirus and Rotavirus antibodies
  - Additional Infectious Agents
  - Vitamin D
  - Alpha-tocopherol, Gamma-tocopherol
  - Carotenoids
  - Ascorbic Acid
- Red blood cell membrane fatty acid
- Buffy Coat (or PBMC from selected subjects)
- RNA
- HbA1c sample if subject meets the following criteria: An HbA1c sample will be drawn at the next TEDDY visit and every visit thereafter from children who are positive at the 9 month visit or later for at least one autoantibody (regardless of autoantibody positivity confirmation or persistence).
- Maternal AA sample if mother has type 1 or 2 diabetes or gestational diabetes and/or child is shown to be autoantibody positive at 3 or 6 months of age – this sample is only collected from the mother one time during the study and can be collected up to the 24 month visit

Nasal Swab
Toenail clippings

In case the optimal proposed blood volume is not available, particularly at the earliest time points, the priorities for blood samples are as follows:

1.	serum	0.1-0.5 mL whole blood volume
2.	plasma, RBC, PBMC	0.6-1.0 mL whole blood volume
3.	mRNA	2.5 mL whole blood volume
4.	Any additional storage	

Instructions/Materials for parent:
Stool sample collection kits (for monthly sample collection at home)
Give new TEDDY Book for years 2-5

27 Month Visit

Forms:
Physical Exam Form
Annual Questionnaire
TEDDY Book Extraction

Procedures:
Height
Weight
Blood Draw (total recommended volume 20.5 ml):
- Serum:
  - Autoantibodies
  - Serum Cytokines/Inflammation markers
- Plasma:
  - Enterovirus and Rotavirus PCR
  - Enterovirus and Rotavirus antibodies
  - Additional Infectious Agents
- Buffy Coat (or PBMC from selected subjects)
- RNA
- HbA1c sample if subject meets the following criteria: An HbA1c sample will be drawn at the next TEDDY visit and every visit thereafter from children who are positive at the 9 month visit or later for at least one autoantibody (regardless of autoantibody positivity confirmation or persistence).

Nasal Swab

In case the optimal proposed blood volume is not available, particularly at the earliest time points, the priorities for blood samples are as follows:

1.	serum	0.1-0.5 mL whole blood volume
2.	plasma, RBC, PBMC	0.6-1.0 mL whole blood volume
3.	mRNA	2.5 mL whole blood volume
4.	Any additional storage	

Instructions/Materials for parent:
Stool sample collection kits (for monthly sample collection at home)
3 day diet record instruction

30 Month Visit

Forms:
Physical Exam Form
3 Day Diet Record
TEDDY Book Extraction

Procedures:
Height
Weight
Blood Draw (total recommended volume 20.5 ml):
- Serum:
  - Autoantibodies

Serum Cytokines/Inflammation markers
Plasma:
Enterovirus and Rotavirus PCR
Enterovirus and Rotavirus antibodies
Additional Infectious Agents
Buffy Coat (or PBMC from selected subjects)
RNA
HbA1c sample if subject meets the following criteria: An HbA1c sample will be drawn at the next TEDDY visit and every visit thereafter from children who are positive at the 9 month visit or later for at least one autoantibody (regardless of autoantibody positivity confirmation or persistence).
Nasal Swab

In case the optimal proposed blood volume is not available, particularly at the earliest time points, the priorities for blood samples are as follows:

1.	serum	0.1-0.5 mL whole blood volume
2.	plasma, RBC, PBMC	0.6-1.0 mL whole blood volume
3.	mRNA	2.5 mL whole blood volume
4.	Any additional storage	

Instructions/Materials for parent:
Stool sample collection kits (for monthly sample collection at home)

33 Month Visit

Forms:
Physical Exam Form
TEDDY Book Extraction
Update form for Primary Caretaker
Update form for Family History Questionnaire

Procedures:
Height
Weight
Blood Draw (total recommended volume 20.5 ml):
Serum:
Autoantibodies
Serum Cytokines/Inflammation markers
Plasma:
Enterovirus and Rotavirus PCR
Enterovirus and Rotavirus antibodies
Additional Infectious Agents
Buffy Coat (or PBMC from selected subjects)
RNA

HbA1c sample if subject meets the following criteria: An HbA1c sample will be drawn at the next TEDDY visit and every visit thereafter from children who are positive at the 9 month visit or later for at least one autoantibody (regardless of autoantibody positivity confirmation or persistence).

Nasal Swab

In case the optimal proposed blood volume is not available, particularly at the earliest time points, the priorities for blood samples are as follows:

1.	serum	0.1-0.5 mL whole blood volume
2.	plasma, RBC, PBMC	0.6-1.0 mL whole blood volume
3.	mRNA	2.5 mL whole blood volume
4.	Any additional storage	

Instructions/Materials for parent:
Stool sample collection kits (for monthly sample collection at home)
3 day diet record instruction
Tap Water Sample instructions and supplies (for collection at home; sample should be brought to 36 month visit)

36 Month Visit

Forms:
Physical Exam Form
3 Day Diet Record
TEDDY Book Extraction
Tracking form: Symptoms of Celiac Disease

Procedures:
Height
Weight
Blood Draw (total recommended volume 25.5 ml):
- Serum:
  - Autoantibodies
  - Serum Cytokines/Inflammation markers
  - Transglutaminase antibodies
  - Additional serum aliquots
- Plasma:
  - Enterovirus and Rotavirus PCR
  - Enterovirus and Rotavirus antibodies
  - Additional Infectious Agents
  - Vitamin D
  - Alpha-tocopherol, Gamma-tocopherol
  - Carotenoids

Ascorbic Acid
Additional plasma aliquots
Red blood cell membrane fatty acid
Buffy Coat (or PBMC from selected subjects)
RNA
HbA1c sample if subject meets the following criteria: An HbA1c sample will be drawn at the next TEDDY visit and every visit thereafter from children who are positive at the 9 month visit or later for at least one autoantibody (regardless of autoantibody positivity confirmation or persistence).
Nasal Swab
Urine
Collect Water Sample brought from home

In case the optimal proposed blood volume is not available, particularly at the earliest time points, the priorities for blood samples are as follows:

1.	serum	0.1-0.5 mL whole blood volume
2.	plasma, RBC, PBMC	0.6-1.0 mL whole blood volume
3.	mRNA	2.5 mL whole blood volume
4.	Any additional storage	

Instructions/Materials for parent:
Stool sample collection kits (for monthly sample collection at home)

39 Month Visit

Forms:
Physical Exam Form
Annual Questionnaire
TEDDY Book Extraction

Procedures:
Height
Weight
Blood Draw (total recommended volume 25.5 ml):
Serum:
Autoantibodies
Serum Cytokines/Inflammation markers
Additional serum aliquots
Plasma:
Enterovirus and Rotavirus PCR
Enterovirus and Rotavirus antibodies
Additional Infectious Agents
Additional plasma aliquots

Buffy Coat (or PBMC from selected subjects)
RNA
HbA1c sample if subject meets the following criteria: An HbA1c sample will be drawn at the next TEDDY visit and every visit thereafter from children who are positive at the 9 month visit or later for at least one autoantibody (regardless of autoantibody positivity confirmation or persistence).
Nasal Swab

In case the optimal proposed blood volume is not available, particularly at the earliest time points, the priorities for blood samples are as follows:

1.	serum	0.1-0.5 mL whole blood volume
2.	plasma, RBC, PBMC	0.6-1.0 mL whole blood volume
3.	mRNA	2.5 mL whole blood volume
4.	Any additional storage	

Instructions/Materials for parent:
Stool sample collection kits (for monthly sample collection at home)
3 day diet record instruction
Salivary cortisol sample instructions and supplies (for collection at home; sample should be brought to 42 month visit)
Child Behavior Checklist

42 Month Visit

Forms:
Physical Exam Form
3 Day Diet Record
TEDDY Book Extraction
Child Behavior Checklist

Procedures:
Height
Weight
Blood Draw (total recommended volume 25.5 ml):
- Serum:
  - Autoantibodies
  - Serum Cytokines/Inflammation markers
  - Additional serum aliquots
- Plasma:
  - Enterovirus and Rotavirus PCR
  - Enterovirus and Rotavirus antibodies
  - Additional Infectious Agents
  - Additional plasma aliquots
- Buffy Coat (or PBMC from selected subjects)

RNA
HbA1c sample if subject meets the following criteria: An HbA1c sample will be drawn at the next TEDDY visit and every visit thereafter from children who are positive at the 9 month visit or later for at least one autoantibody (regardless of autoantibody positivity confirmation or persistence).
Nasal Swab
Urine
Collect salivary cortisol sample brought from home and collect the two additional salivary cortisol samples in clinic

In case the optimal proposed blood volume is not available, particularly at the earliest time points, the priorities for blood samples are as follows:

1. serum 0.1-0.5 mL whole blood volume
2. plasma, RBC, PBMC 0.6-1.0 mL whole blood volume
3. mRNA 2.5 mL whole blood volume
4. Any additional storage

Instructions/Materials for parent:
Stool sample collection kits (for monthly sample collection at home)

45 Month Visit

Forms:
Physical Exam Form
TEDDY Book Extraction
Update form for Primary Caretaker

Procedures:
Height
Weight
Blood Draw (total recommended volume 25.5 ml):
Serum:
Autoantibodies
Serum Cytokines/Inflammation markers
Additional serum aliquots
Plasma:
Enterovirus and Rotavirus PCR
Enterovirus and Rotavirus antibodies
Additional Infectious Agents
Additional plasma aliquots
Buffy Coat (or PBMC from selected subjects)
RNA
HbA1c sample if subject meets the following criteria: An HbA1c sample will be drawn at the next TEDDY visit and every visit thereafter from

children who are positive at the 9 month visit or later for at least one autoantibody (regardless of autoantibody positivity confirmation or persistence).

Nasal Swab

In case the optimal proposed blood volume is not available, particularly at the earliest time points, the priorities for blood samples are as follows:

1.	serum	0.1-0.5 mL whole blood volume
2.	plasma, RBC, PBMC	0.6-1.0 mL whole blood volume
3.	mRNA	2.5 mL whole blood volume
4.	Any additional storage	

Instructions/Materials for parent:
Stool sample collection kits (for monthly sample collection at home)
3 day diet record instruction
Toenail clipping pre-visit instructions

48 Month to 15 Year Visits

At 4 years of age and beyond those children who have been deemed persistent autoantibody positive will follow a 3 month visit schedule (confirmation results from the confirmatory Autoantibody lab will not be taken into consideration for determining the subject's visit schedule, only the local lab's results will be used for this); all other subjects will attend clinic visits every 6 months beginning at 4 years of age until age 15. For subjects who become autoantibody positive at 4 years of age or older, the subject will be reinstated on the three month visit schedule at the first indication of autoantibody positivity and will stay on if persistent. If the next available sample is negative, thus the subject is not deemed persistent autoantibody positive, the subject will be seen every 6 months instead of every 3 months from that point on. Subjects who have been persistently single autoantibody positive, but who become negative to all antibodies for 1 year or more will be placed on the biannual visit schedule after 4 years of age. Subjects who have been persistently multiple autoantibody positive, but who become negative to all antibodies for 1 year or more will remain on the three month visit schedule.

Forms to be done every three months:
Physical Exam Form
TEDDY Book Extraction

Forms to be done every six months:
Physical Exam Form
3 Day Diet Record - *In August 2018, the collection protocol was changed so as to continue to collect 3 day diet records every 6 months from subjects who are single or multiple persistent confirmed autoantibody positive (even if the subject reverts to autoantibody negativity) and to stop 3 day diet record collections on all other subjects after the 10 year visit. Should a subject be deemed single or multiple persistent*

confirmed autoantibody positive after the 10 year visit, the 3 day diet record collection will be restarted at the next visit.
TEDDY Book Extraction

Forms only to be done yearly:
Annual Parent Questionnaire through 14 year visit
End of TEDDY Parent Questionnaire at 15 year visit
Tracking form: Symptoms of Celiac Disease

Forms only to be done every two years:
Update form for Primary Caretaker

Forms only to be done every four years:
Update form for Family History Questionnaire

Procedures to be done every three months:
Height
Weight
Blood Draw (total recommended volume at least 30.5 ml at 48 month visit and at least 25.5 ml at 51 month visit through 15 year visit - as children get older additional blood volume will be collected based upon local IRB/Ethics Board approval and the weight of the child. At no time will the blood draw volume exceed what is allowable according to the subject's body weight - 3 mL/kg per visit):

- Serum:
  - Autoantibodies
  - Serum Cytokines/Inflammation markers
  - Additional serum aliquots
- Plasma:
  - Enterovirus and Rotavirus PCR
  - Enterovirus and Rotavirus antibodies
  - Additional Infection Agents
  - Additional plasma aliquots
- Buffy Coat (or PBMC from selected subjects)
- RNA
- HbA1c sample if subject meets the following criteria: An HbA1c sample will be drawn at the next TEDDY visit and every visit thereafter from children who are positive at the 9 month visit or later for at least one autoantibody (regardless of autoantibody positivity confirmation or persistence).

Nasal Swab

In case the optimal proposed blood volume is not available, particularly at the earliest time points, the priorities for blood samples are as follows:

1. serum 0.1-0.5 mL whole blood volume
2. plasma, RBC, PBMC 0.6-1.0 mL whole blood volume

3. mRNA 2.5 mL whole blood volume
4. Any additional storage

Procedures to be done every six months:

Height
Weight
Blood Draw (total recommended volume at least 30.5 ml at 48 month visit and at least 25.5 ml at 54 month visit through 15 year visit - as children get older additional blood volume will be collected based upon local IRB/Ethics Board approval and the weight of the child. At no time will the blood draw volume exceed what is allowable according to the subject's body weight - 3 mL/kg per visit):

Serum:
- Autoantibodies
- Serum Cytokines/Inflammation markers
- Additional serum aliquots

Plasma:
- Enterovirus and Rotavirus PCR
- Enterovirus and Rotavirus antibodies
- Additional Infection Agents
- Additional plasma aliquots

Buffy Coat (or PBMC from selected subjects)
RNA
HbA1c sample if subject meets the following criteria: An HbA1c sample will be drawn at the next TEDDY visit and every visit thereafter from children who are positive at the 9 month visit or later for at least one autoantibody (regardless of autoantibody positivity confirmation or persistence).

Nasal Swab
Urine

In case the optimal proposed blood volume is not available, particularly at the earliest time points, the priorities for blood samples are as follows:

1. serum 0.1-0.5 mL whole blood volume
2. plasma, RBC, PBMC 0.6-1.0 mL whole blood volume
3. mRNA 2.5 mL whole blood volume
4. Any additional storage

Procedures only to be done yearly:

Physical Activity Assessment – at 5 years of age done every year at the annual visit - *In August 2018, the collection protocol was changed so as to continue to collect physical activity assessments annually from subjects who are single or multiple persistent confirmed autoantibody positive (even if the subject reverts to autoantibody negativity) and to stop physical activity assessments on all other subjects after the 10 year visit. Should a subject be deemed single or multiple persistent confirmed autoantibody*

positive after the 10 year visit, the physical activity assessment will be restarted at the next visit.

Toenail samples –done every one year at the annual visit

Serum:

Transglutaminase antibodies

Plasma:

Vitamin D
Alpha-tocopherol, Gamma-tocopherol
Carotenoids
Ascorbic Acid

Red blood cell membrane fatty acid

Procedures only to be done every two years:

Water samples – at 5 years of age done every two years at the annual visit

Procedures only to be done at the 4.5 year visit and the 5.5 year visit:

Child Behavior Checklist
Collect salivary cortisol sample brought from home and collect the two additional salivary cortisol samples in clinic

Procedures only to be done at the 8 year visit and the 14 year visit:

Thyroid samples

Instructions/Materials for parent:

Stool sample collection kits (for sample collection at home every 3 months until 10 years of age and every 6 months thereafter - *in August 2018 all stool sample collections were stopped on all subjects*)
3 day diet record instruction
New TEDDY Book for subsequent years of child as determined
Toenail clipping pre-visit instructions –done every one year at the annual visit
Tap Water Sample instructions and supplies – at 5 years of age done every two years at the annual visit
Salivary cortisol sample instructions and supplies (for collection at home; sample should be brought to the 4.5 year visit and the 5.5 year visit)
Child Behavior Checklist to be brought to the 4.5 year visit and the 5.5 year visit

4 Year Visit

Everything as listed in the 48 month to 15 year visit in addition to the following procedure.

Procedures:

Whole Blood for Non-HLA genotyping - A whole blood sample will be drawn from subjects at the 4 year clinic visit. If the sample cannot be collected at the 4 year visit, it

should be attempted to be collected at the next scheduled visit, but must be collected by the 5 year 9 month visit.

10 Year to 15 Year Visit

Everything as listed in the 48 month to 15 year visit in addition to the following form.

Forms:
Annual Child Questionnaire (completed annually through 14 year visit)
End of TEDDY Child Questionnaire completed at 15 year visit
Parent Strengths and Difficulties Questionnaire (completed at the 11 year 6 month visit and 13 year 6 month visit)
Child Strengths and Difficulties Questionnaire (completed at the 11 year 6 month visit and 13 year 6 month visit)

8 Year to 15 Year Visit

Everything as listed in the 48 month to 15 year visit in addition to the following forms.

Forms:
Pubertal Assessment Status Form (completed every 6 months until pubertal status is assessed as Stage 5 for both pubic hair and breast development/genitalia or the child reaches 15 years of age.)

9.3.1 Antibody Test Result additions:

If Child Tests Positive For Any Autoantibody
Procedures to be done at every visit:
Random plasma/blood glucose

A clinical center may stop doing random glucose measurements on a subject who meets the following criteria:

There has been only 1 positive antibody sample in the child's life (excluding maternal transfer of autoantibodies)

AND

There have been 2 consecutive negative antibody samples after the positive.

If Child Does Develop Two or More Antibodies (regardless of antibody positivity confirmation or persistence): From 36 Months onward
Procedures to be done every six months:
Oral Glucose tolerance test (OGTT)

9.4 Informed Consent Procedures

The model informed consent for follow-up was developed and approved by the EEC (in Section 7 appendix D) and then clinical centers tailored this model to the procedures and language requirements of their local IRBs. All local informed consents and current IRB approval letters must be on file with the DCC for a clinical center to be operating.

Training Requirements:

- Local staff administering the informed consents must take the required Human Subjects and HIPAA courses and obtain a certificate of completion at sites where this is a requirement.
- Training must also include either taking part in the centralized training sessions or viewing the appropriate videos and PowerPoint presentations of these training sessions on the web.
- Practice sessions with experienced person role playing subject and an observer present to give feedback.
- Observation of administration with real subjects.
- Review and discussion of the frequently asked questions document.

9.5 Transfer of TEDDY Eligible Participants between Study Sites

If a family moves to another participating site while in TEDDY, the TEDDY subject can transfer to that site. In order to maintain the confidentiality of study related information, a TEDDY subject can only be assigned to one site at a time. Once it has been determined that the TEDDY participant will transfer, there needs to be communication between the two involved sites. The receiving site should be given the following information from the original site:

1) Name, Subject ID and Local Code
2) Address and contact phone number(s)
3) Date of Birth
4) Parent's names
5) Estimated date of arrival to new TEDDY site
6) HLA genotype, islet autoantibody values and transglutaminase antibody values from each visit leading up to time of transfer
7) General report of any outstanding family issues or TEDDY compliance that may be useful to the receiving site.
8) Gender
9) Race
10) Ethnicity
11) Family history of type 1 diabetes
12) If the transfer is before the 3 month visit, the date the family was informed of the HLA risk (for the new site to indicate on the enrollment form)

Because a subject can only be associated with one clinical center, it is only possible for one site (clinical center that the subject is currently assigned to in the DCC's database) to view the subject's Participant Details Page on the TEDDY website (www.teddy.epi.usf.edu). Because of this, the original site should ensure that each form has been submitted and each sample has been collected (that is required up to that point in time) and shipped to either the corresponding lab or the Repository. Samples must be shipped prior to the transfer of the subject in the DCC's database

so that the vial(s) numbers will appear on the shipment log and so that the shipment date will be indicated properly in the DCC's database. If it is not possible to collect the form or the sample, the 'not done' reason should be indicated in the tracking system before the transfer takes place. The transferring site should also be sure to review the Error Reporting and Verification System and address any errors for the transferring subject indicated in the system at that time. Once all samples and forms are accounted for and discrepancies indicated in the Error Reporting and Verification System have been cleared up, the DCC should be notified of the transfer. At the time of transfer, the task status (listed on the subject's Participant Details Page) of every form and sample (that should have been collected up to that point in time) should not be blank, it should be populated with either "Complete", "Incomplete" or "Not done". **Because the original site will lose access to the Participant Details Page at the time of the transfer, a blank task status field is not acceptable at time of the transfer**. Exceptions to this are: two of the three First Questionnaires (information for at least one First Questionnaire must be submitted), a second 6 month Questionnaire (information for at least one 6 month Questionnaire must be submitted), a second 9 month Interview (information for at least one 9 month Interview must be submitted), the Maternal Autoantibody Sample, the 9 month HLA confirmation sample, a second Annual Questionnaire (information from at least one Annual Questionnaire must be submitted), the Salivary Cortisol Sample and Salivary Cortisol parent and staff forms (if the site the subject is transferring from is not participating in the Salivary Cortisol Sub-study). The original site is the only site to hold the information to resolve the blank field; therefore, it must be completed before the transfer takes place. The DCC will monitor this and not complete the transfer until all issues have been resolved.

Error Corrections After Transfer – Any errors appearing in the Error Reporting and Verification System (ERVS) after transfer should be handled in the following way:

1. The receiving site should notify the transferring site of any errors that appear in the ERVS for the transferred subject. Since only the receiving site can view the errors, the receiving site should be sure to send all of the details of the error to the transferring site.
2. The transferring site should review the child's original source documentation to determine if the reported errors should be corrected or verified and provide the receiving site with this information. If any information needs to be corrected on the original source documentation, the transferring site should make the correction and be sure to initial and date next to the change.
3. The receiving site should use the ERVS to correct or verify the data as indicated by the transferring site.

9.6 Adverse Event Reporting

TEDDY is an observational, non interventional, study and no greater than minimal risk is anticipated. The probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests. It is the responsibility of each center to report adverse events associated with study participation and any serious adverse events experienced by the participant to the DCC and their respective review/monitoring boards.

An Adverse Event (AE) is defined for the TEDDY study as "…an unfavorable and unintended sign, symptom or disease **associated** with a subject's participation in the TEDDY study." This definition encompasses any **untoward serious** occurrence (physical, psychological, behavioral) that occurs during the course of the study **regardless** of its relationship to the Study. A Serious Adverse Event (SAE) includes those events that: "…result in death; are life-threatening; require inpatient hospitalization or prolongation of existing hospitalization; create persistent or significant disability/incapacity, or a congenital anomaly/birth defects." An Unexpected Adverse Event is defined as any adverse experience for which the specificity or severity of is not consistent with the risks of information described in the protocol. Therefore an Expected Adverse Event is identified in the research protocol as having been previously associated with or having the potential to arise as a consequence of participation in the study.

The TEDDY protocol calls for each Adverse Event to be reported and filed in specialized online forms that can be found on the TEDDY website (see specific instructions below in section entitled "Reporter instructions for using the online TEDDY Adverse Event System"). The FDA provides guidance on data elements and values sets that should be included and are required for reporting. The CTCAE v.3 contains reporting criteria in widespread use as a standard in oncology, and has been adapted for use here in TEDDY.

The DCC has developed and monitors an Adverse Event System located on the TEDDY members' website that enables a specified reviewer(s) to access and review information on reported Adverse Events. The system is designed to electronically capture data on reported Adverse Events, forward it to the AE reviewer, and organize the communication and subsequent actions (if applicable) related to each reported Adverse Event.

At the occurrence of a reportable Adverse Event, the research staff at the local site will enter the data into the online Adverse Event System (in general, reporting of Adverse Events should happen in a timely manner consistent with other reporting requirements). The automated system will forward the reported information (via email) to the AE reviewer. That email message will contain a hyperlink to the login to review the Adverse Event. The AE reviewer may use the system to request further information if necessary, to determine causality, and possibly recommend changes to the protocol or consent forms as a consequence of the Adverse Event. After the AE reviewer has reviewed the Adverse Event, the online system provides options to: close the Adverse Event case, request further/follow-up information, or request a meeting or further discussion with study investigators. The Adverse Event System maintains audit trails and stores data (and data updates) and communication related to any Adverse Event. The PI of the clinical center that reported the Adverse Event is automatically informed via email of all Adverse Events as they are reported to the Adverse Event System. The Adverse Event review process takes place in near real-time, as the entire reporting and review is done by automatically generated emails. The DCC will submit aggregate reports of all Adverse Events to the PIs.

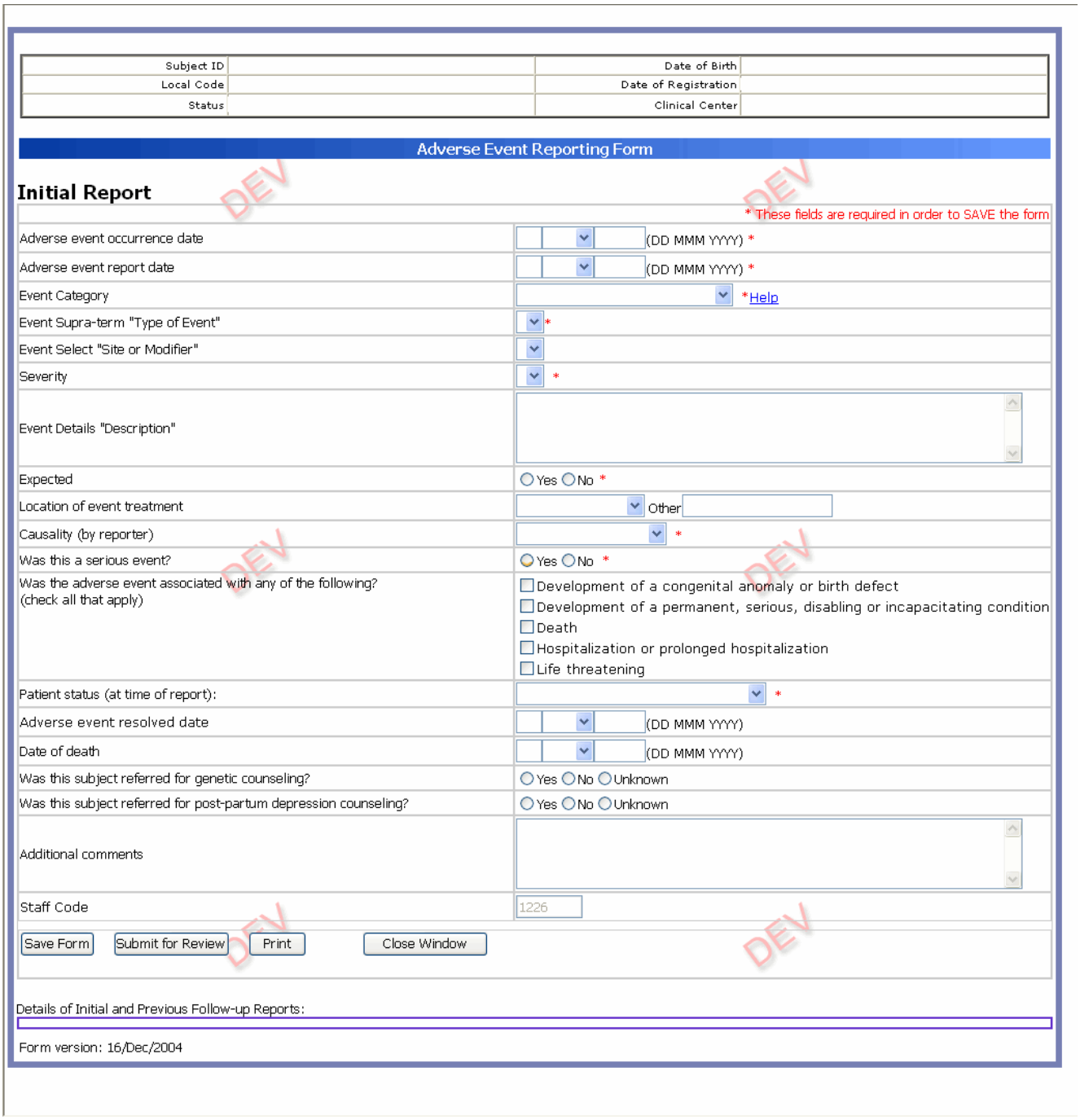
Additional individuals (specified by the Steering Committee or NIH) can be automatically notified of all Adverse Events, although they have no network responsibilities in the Adverse Event review. An Administrator at the DCC monitors the use of the system and can manually assign Adverse Events to Reviewers or re-assign Adverse Events to other Reviewers if the Adverse Event is not

reviewed in a reasonable time frame. The Administrator also assigns the roles (e.g. Reviewer, Reader) to individuals using the system.

Each clinical center is responsible for reporting adverse events to their respective IRB or monitoring boards in a format and according to their institution's requirements.

Reporter Instructions for using the online TEDDY Adverse Event System:

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject that you would like to report the Adverse Event for by entering one of the following: 1) Local Code and Subject ID 2) Local Code and Date of Birth 3) Date of Birth Range 4) Clinical Center and Subject ID 5) Clinical Center and Local Code or 6) Clinical Center and/or Visit Location Code.
4. Under "Search Results", click on the Local Code of the desired subject.
5. Go to the "Additional Study Forms" dropdown near the top right of the screen.
6. Choose "Adverse Event" from the dropdown menu and click on the "Select Form" button directly under the dropdown menu.
7. A form entitled "Adverse Event Reporting Form" will open in a new window (see example of form below) – you must fill out the information on this form in order to report an Adverse Event. The fields with a red asterisk next to them are required in order to save the form. See Table 9.1 for the specifics of each field. To save this report, click on the "Save Form" button at the bottom of the form. If the save is successful, you will see "Form Successfully Saved" in a pop-up window in the middle of the screen. If you close the window at this point, you may come back to this form and make further changes before you submit the report for review (see "Viewing/Submitting/Editing previously reported adverse events" below). To submit this report for review, click "Submit for Review". This will lock the form from further editing - to submit a change, you will be required to submit a follow-up report (see "Viewing/Submitting/Editing previously reported adverse events" below). You will be contacted by the DCC if additional information is requested by the AE reviewer.



Subject ID		Date of Birth	
Local Code		Date of Registration	
Status		Clinical Center	

Adverse Event Reporting Form

Initial Report

DEV DEV

* These fields are required in order to SAVE the form

Adverse event occurrence date	(DD MMM YYYY) *
Adverse event report date	(DD MMM YYYY) *
Event Category	*Help
Event Supra-term "Type of Event"	*
Event Select "Site or Modifier"	
Severity	*
Event Details "Description"	
Expected	Yes No *
Location of event treatment	Other
Causality (by reporter)	*
Was this a serious event?	Yes No *
Was the adverse event associated with any of the following? (check all that apply)	Development of a congenital anomaly or birth defect Development of a permanent, serious, disabling or incapacitating condition Death Hospitalization or prolonged hospitalization Life threatening
Patient status (at time of report):	*
Adverse event resolved date	(DD MMM YYYY)
Date of death	(DD MMM YYYY)
Was this subject referred for genetic counseling?	Yes No Unknown
Was this subject referred for post-partum depression counseling?	Yes No Unknown
Additional comments	
Staff Code	1226

DEV DEV DEV DEV

Save Form | Submit for Review | Print | Close Window

Details of Initial and Previous Follow-up Reports:

Form version: 16/Dec/2004

Table 9.1 Data Collected, Constraints, and Standards Applied

Data Element	Constraints	Values	Notes
Adverse Event Occurrence Date	required	Valid date	--
Adverse Event Report Date	required	Valid date	--
Event Category	required	CTCAE (v3) categories - click on the 'help' link on the AE reporting form for details	--
Event Supra-term ("Type of Event")	required	CTCAE (v3)	--
Event Select "Site or Modifier"	optional	CTCAE (v3)	--
Severity	required	CTCAE (v3)	--
Event Details "Description"	optional	Free text description	--
Expected	required	Yes/No	--
Location of event treatment	optional	Outpatient; Inpatient; Emergency room; None; Unknown	--
Causality (by reporter)	required	Definitely not related; Probably not related; Possibly related; Probably related; Definitely related	Causality is assessed by the DSMB reviewer; this is a supplemental assessment of causality by reporter and is optional
Was this a serious event?	required	Yes/No	--
Was the adverse event associated with any of the following? (check all that apply)	optional	Development of a congenital anomaly or birth defect; Development of a permanent serious, disabling or incapacitating condition; Death; Hospitalization or prolonged hospitalization; Life threatening	--
Patient status (at time of report)	required	Fatal; Intervention for AE continues; Not recovered/Not resolved; Recovered/Resolved with sequelae; Recovered/Resolved without Sequelae; Recovering/Resolving; Unknown	--
AE resolved date	optional	Valid date	--

Date of Death	required if Patient status = 'fatal'	Valid date	--
Was this subject referred for genetic counseling?	optional	Yes/No/Unknown	--
Was this subject referred for post-partum depression counseling?	optional	Yes/No/Unknown	--
Additional comments	optional	--	--

Viewing/Submitting/Editing previously reported Adverse Events (clinical center)

Once the Participant's Details Page has been refreshed, you will see "Adverse Event" under "Completed Additional Study Forms" near top of Participant's Details Page:

1. Click on this form link, entitled "Adverse Event" under "Completed Additional Study Forms".
2. A new window will open entitled "Adverse Event Form List" which lists all of the previously reported Adverse Events for this participant.
3. If you would like to view a report that has been submitted for review click on the "view" link in the "Action" column.
4. If you would like to view/edit a report that has been saved, but NOT submitted for review, click on "Edit/Submit" report, make your changes, and save or submit the report.
5. If you would like to Submit for Review an event that was previously entered, click on "Edit/Submit" report, then click the "Submit for Review" button.
6. If you would like to report a new follow-up for an AE that has been submitted for review select the link "Report new follow-up" in the "Action" column. Enter the new information and click on the "Save Form" button at the bottom of the form (note: you must enter a follow-up date and reason on all follow-up reports). If the save is successful, you will see "Form Successfully Saved" in a pop-up window in the middle of the screen. To submit this follow-up report for review, click the "Submit for Review" button.

NOTE: If you have been contacted by the DCC about a request from the AE Reviewer for additional information – you should provide this additional information by reporting a new follow-up by following the instructions above in the section on "Viewing/Submitting/Editing previously reported Adverse Events".

AE Reviewer Instructions for using the online TEDDY Adverse Event System:

Email notification to AE Reviewer

The automated Adverse Event System forwards an email notification of the reported adverse event to the AE reviewer. This email notification contains information regarding the Adverse Event and also contains a link to the online Adverse Event System, where the AE Reviewer will login to review the AE.

Adverse Event Review System

The AE reviewer can get to the AE Review System via two different methods:

- By clicking on the link provided in the automatic email notification:
  1. After clicking on the link in the automatic email notification the AE reviewer will be directed to provide their TEDDY website login information.
  2. The reviewer will be directed to a "Review Adverse Event" form. This form displays a summary of the event, as well as a space (at the bottom of the form) for you to enter causality, recommended changes to the protocol and/or consent form, additional comments and if additional information is required or not. The asterisked fields are required. You may click on the first link on the bottom of this form to view all adverse events for this participant. The second link will display the Participant's Details page with a list of data forms and sample information available for viewing. To save the review, click on the "Save" button at the bottom of the form. If the save is successful, you will see "Form Successfully Saved" in a pop-up window in the middle of the screen. You may then close this window.

- By going to the TEDDY website and logging in:
  1. Logon to the TEDDY website http://teddy.epi.usf.edu/
  2. To review Adverse Events, click on the "Review Adverse Events" link located on the left navigation menu under "Administration".
  3. A window will open entitled "Adverse Event Review System"; the window displays two tabs, one entitled "Awaiting Review" and the other entitled "Previously Reviewed".
  4. To review an event in the "Awaiting Review" category, click on that tab and then click the "Review" link in the "Action" column.
  5. You will be directed to a "Review Adverse Event" form. This form displays a summary of the event, as well as a space (at the bottom of the form) for you to enter causality, recommended changes to the protocol and/or consent form, additional comments and if additional information is required or not. The asterisked fields are required. You may click on the first link on the bottom of this form to view all adverse events for this participant. The second link will display the Participant's Details page with a list of data forms and sample information available for viewing. To save the review, click on the "Save" button at the bottom of the form. If the save is successful,

you will see "Form Successfully Saved" in a pop-up window in the middle of the screen. You may then close this window.

6. To view events already reviewed, click on the "Previously Reviewed" tab in the "Adverse Event Review System" window.
7. Click on the "View Review" link in the "Action" column to look at the review of the event (you can also modify the review here - just be sure to save upon completion.)
8. You will be directed to a "Review Adverse Event" form. The form will display the information previously entered by the reviewer.

9.7 Reporting of Referrals for Genetic Counseling and Post-partum Depression Counseling

The online Adverse Event Reporting Form should also be used to report referral of a subject for Genetic Counseling and/or Post-partum Depression Counseling.

An answer of 'yes' should be indicated to the question 'Was this subject referred for post-partum depression counseling?' whenever a TEDDY staff member offers a parent a referral to a specialist due to a high post-partum depression score. This is regardless of whether the parent actually accepts the offer or if the parent is already being seen by a specialist for post-partum depression. No matter what the outcome, if the TEDDY staff member offers a referral to a specialist 'yes' should be indicated to this question on the AE form.

Instructions for using the online Adverse Event Reporting Form for counseling referral:

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject that you would like to report the Adverse Event for by entering one of the following: 1) Local Code and Subject ID 2) Local Code and Date of Birth 3) Date of Birth Range 4) Clinical Center and Subject ID 5) Clinical Center and Local Code or 6) Clinical Center and/or Visit Location Code.
4. Under "Search Results", click on the Local Code of the desired subject.
5. Go to the "Additional Study Forms" dropdown near the top right of the screen.
6. Choose "Adverse Event" from the dropdown menu and click on the "Select Form" button directly under the dropdown menu.
7. A form entitled "Adverse Event Reporting Form" will open in a new window – to report a counseling referral the following information must be provided: AE occurrence date, AE report date and answers to the two counseling referral questions.
8. To save this report, click on the "Save Form" button at the bottom of the form. If the save is successful, you will see "Form Successfully Saved" in a pop-up window in the middle of the screen. If you close the window at this point, you may come back to this form and make further changes before you submit the report for review (see "Viewing/Submitting/Editing previously reported adverse events" in section 9.6). To submit this report for review, click "Submit for Review". This will lock the form from further editing - to submit a change, you will be required to submit a follow-up report (see "Viewing/Submitting/Editing previously reported adverse events" in section 9.6).

Section 9 – Appendix:

A. **Diabetes Informational Card**
B. **Normal Development for Children (Ages Birth-Five years)**
C. **Activities for 3 month old TEDDY babies**
D. **Activities for 6 month old TEDDY babies**
E. **Activities for 9 month old TEDDY babies**
F. **Activities for 12 month old TEDDY babies**
G. **Finland's MOO instructions for distribution of the First Junior Scientist Information Packet and Parent Letter**
H. **Sweden's MOO instructions for distribution of the First Junior Scientist Information Packet and Parent Letter**
I. **Georgia/Florida's MOO instructions for distribution of the First Junior Scientist Information Packet and Parent Letter**
J. **Germany's MOO instructions for distribution of the First Junior Scientist Information Packet and Parent Letter**
K. **Washington's MOO instructions for distribution of the First Junior Scientist Information Packet**
L. **Colorado's MOO instructions for distribution of the First Junior Scientist Information Packet**

Appendix A: Diabetes Informational Card

Early symptoms of diabetes can be subtle and develop slowly or during a mild infection. One of the goals of TEDDY is to ensure that children with diabetes symptoms are checked as soon as possible. This helps to prevent complications at the onset of diabetes.

Symptoms of diabetes include:

- **Urinating much more frequently than usual**
- **Drinking more fluids than usual**
- **Losing weight**

Please contact your pediatrician and your **TEDDY Study Clinic** if you think your child is showing symptoms. If your child is diagnosed with diabetes, please show the health care provider the reverse side of this card.

Call XXX.XXX.XXXX

TEDDY

The Environmental Determinants of Diabetes in the Young

Dear Health Care Provider:

If you have just diagnosed a child participating in the TEDDY study with diabetes **it is important to our study** to obtain initial laboratory values.

In addition to documenting the presence of polydipsia, weight loss or lack of weight gain, and polyuria, please document the height and weight of the child and consider obtaining as many of the following labs as is clinically indicated:

- **Serum pH**
- **Urine ketones and/or blood ketones**
- **Basic metabolic profile with serum bicarbonate**
- **HbA1c**

Call XXX.XXX.XXXX

with any questions

TEDDY

The Environmental Determinants of Diabetes in the Young

Appendix B: Normal Development for Children (Ages Birth-Five years)

1 month:
-able to raise head from surface when lying on tummy
-pays attention to someone's face in their direct line of vision
-moves arms and legs in an energetic manner
-likes to be held and rocked

2 months:
-smiles and coos
-rolls part way to side when lying on back
-grunts and sighs

3 months:
-eyes follow a moving object
-able to hold head erect
-grasps object when placed in their hand
-babbles

4 months:
-holds a rattle for an extended period of time
-laughs out loud
-sits supported for short periods of time
-recognizes bottle and familiar faces

5 months:
-reaches for and holds objects
-stands firmly when held
-stretches out arms to be picked up
-likes to play peek-a-boo

6 months:
-turns over from back to stomach
-turns toward sounds
-sits with a little support
-persistently reaches for objects out of reach
-listens to own voice
-coos and squeals
-grasps and mouths objects
-hold, sucks, bites cracker, begins chewing

7 months:
-can transfer object from one hand to another
-can sit for a few minutes without support
-pats and smiles at image in mirror
-creeps
-is shy at first with strangers

8 months:
-can sit steadily for about 5 minutes
-crawls
-grasps things with thumb and first 2 fingers
-likes to be near parent

9 months:
-says mama or dada
-responds to name
-can stand for a short time holding on to support
-able to hit 2 objects together on their own
-copies sounds

10 months:
-able to pull up
-can drink from a cup when it's held

11 months:
-can cruise (ie walk holding on to furniture)
-can find an object placed under another object

12 months:
-waves bye-bye
-can walk holding someone's hand
-says 2 words besides mama or dada
-eats some solid foods
-finger feeds themselves
-likes to have an audience

15 months:
-walks by themselves
-shows wants by pointing and gesturing
-scribbles on paper after shown how to do that
-begins using a spoon
-cooperates with dressing

18 months:
-can build a tower of 3 blocks
-likes to climb and take things apart

-can say 6 words
-tries to put on shoes
-drinks from cup held in both hands
-likes to help parent

2 years:
-able to run
-says at least 50 words
-sometimes uses 2 word sentences
-points to objects in a book

3 years:
-can repeat 2 numbers in a row
-knows his/her sex
-dress self except for buttoning
-can copy a circle
-can follow 2 commands of on, under or behind (ex. Stand on the rug)
-knows most parts of the body
-jumps lifting both feet off the ground
-can build tower with 9 blocks

4 years:
-can repeat a simple 6 word sentence
-can wash hands and face without help
-can copy a cross-
-can stand on one foot
-can catch a tossed ball

5 years:
-can follow three commands
-can copy a square
-can skip

Appendix C: Activities for 3 month old TEDDY babies

Focus: tactile experiences, touch, stroke, massage. Squeaky toys, gentle sounds, animal noises, soft whistles, chimes, etc. Human faces, bright colors.

Different Drums

It's quite a thrill (for her, at least!) when your baby reaches the banging age. Seeing that one pound of her fist can make a satisfying whomp *is a powerful affirmation that actions can get results. Make it a bang-up time by giving her a range of high and low notes to aim for.*

Skills developed: auditory, sense of rhythm, sense of cause and effect
What you'll need: empty oatmeal containers, ice cream tubs, coffee cans, or any other container with a flexible cardboard or plastic lid; plastic wrap

Make a few drums with different sounds so your baby can hear the difference between deeper and shallower tones. Turn any can or round-shaped container into a drum by stretching several layers of strong plastic wrap or a piece of thick paper over the top and taping it down. Or, even easier, use containers that already have drummable lids, such as Tupperware and oatmeal canisters. Tape the different drums together with duct or packing tape to make a drum set. Sit on the ground facing your baby and place the drums between you. Demonstrate how to tap the drums with your palms, fingers, and the heel of your hand. You might even try singing some doo-wops to demonstrate different rhythms as you play.

Variation: If your baby can grasp, make homemade drumsticks too. Chopsticks are ideal, but wrapped pencils will do just fine. Use some cotton or tissue paper and wad it around the ends of the sticks, then wrap it up in masking tape. Show your baby how to tap the drumsticks on both the tops and sides of the drums. Pretty soon you'll have your own rhythm section going.

Kicking Back

As your baby becomes more mobile, kicking is one of his favorite ways to exercise his restless limbs. And kicking in water — and feeling the water splash — is a wonderfully wet lesson in cause and effect.

Skills developed: gross motor, sense of cause and effect
What you'll need: a bathtub

Fill the bathroom tub or a small baby bathtub with four to six inches of water (no more). Lie your baby down in the water on his back, keeping your hand under his head to keep the water out of his ears and, even more important, his face out of the water. Most babies love the stimulation of the water and the new bathing position and start kicking their legs delightedly. The more they kick, the higher the splashes, and as they discover that it's their legs that are causing all the splashing, watch out!

Pop! Song

Your baby is just beginning to figure out that certain words mean what they sound like. Here's a singing game that makes that point while catering to babies' love of surprises.

Skills developed: verbal, sense of cause and effect
What you'll need: no equipment necessary

Sing the classic nursery song "Pop! Goes the Weasel," but highlight the element of surprise with sound effects and actions. Start out softly and slowly: "'Round and 'round the cobbler's bench, the monkey chased the weasel, the monkey thought 'twas all in fun..." (then raise your voice to finish): "Pop! goes the weasel." Try it again, clapping your hands sharply on the word "pop." Now go again, this time slapping your hand lightly on the floor or a nearby padded surface such as a bed or chair. Grab a stuffed animal and make it jump up into the air on the word "pop." This song can work wonders as a distraction during diaper changes and is also great for keeping your baby awake on short car rides when you don't want him to nap just yet.

Bend Over Butterfly

At 3 months, babies are just becoming fascinated with animals and insects, and pretending to be one together is a great way to pique that interest.

Skills developed: verbal, motor
What you'll need: no equipment needed

Sit cross-legged on the floor or ground with your baby sitting in your lap facing forward (away from you). Bend from the waist with your arms stretched forward, making a roof over your baby with your body, so you become a "cocoon" enveloping her. Encourage her to bend over with you. Speaking softly and slowly, say, "Okay caterpillar, you're waking up now." Gradually lift your arms over your head as you say, "You're coming out of your cocoon now, you're becoming a butterfly." Then sit up and reach your baby's arms up, too. Move your arms out to the sides and flap them, saying, "Now you're spreading your wings — you're a butterfly!" As you play this game over and over, your baby will learn to flap her arms to "be a butterfly" too.

Variation: Once your baby starts walking, she can crawl into your lap as the caterpillar ready to make a cocoon, then stand up and "fly" out of your lap when she's a butterfly, continuing to wave her arms as she moves around the room.

Flashlight Dance

Ever watch your baby turn her gaze to follow a patch of sunlight on the wall? Cater to her captivation with light and dark by playing a soothing bedtime game.

Skills developed: visual, sense of cause and effect
What you'll need: a flashlight with a relatively strong beam

Think of how hypnotizing it is to watch a searchlight sweep the night sky. You can achieve this same effect with a flashlight in a darkened room. When it's time for lights out, hold your baby or sit with her on your lap (this works well in a rocking chair). Shine the flashlight beam slowly over the walls and ceiling, encouraging your baby to follow the moving light with her eyes. Many babies find this very relaxing; you can even create a soothing sound and light show by playing quiet music at the same time or by telling a story about traveling among the stars.

Roller Coaster

Now that he's strong enough to hold his head steady, your baby is learning how to control and manipulate his upper body in preparation for learning to sit, roll over, and — eventually — stand. This game helps develop full-body coordination and makes a great relaxation routine when it's time to wind down before bed.

Skills developed: gross motor
What you'll need: a beach ball or cylindrical bolster pillow

If you're using a beach ball, blow it up most of the way, so it rolls but still has a soft spot. Holding your baby securely with your hands on either side of his rib cage, place him tummy-down on top of the ball or pillow and roll him back and forth and from side to side. Note: A cylindrical bolster pillow provides a gentle, soothing ride, but won't allow the side-to-side action.

Look Who's Here!

Babies just getting the hang of cause and effect are delighted whenever something unexpected pops into the mix. The surprise of seeing your face triggers the biggest giggles — make it an even sillier sight-gag by using a range of goofy expressions.

Skills developed: sense of cause and effect, object permanence
What you'll need: something to hide behind

While your baby is on the changing table (securely strapped, of course), duck down below the side, then pop up with an exaggerated smile or round-eyed "surprise face" and see if you get a giggle out of her. Repeat it with different expressions on your face each time you reappear; this can go on until your facial muscles get tired. When she's in her car seat, duck down behind the back where she can't see you, then appear suddenly over her head so

you're upside down over her. Again, try this with a variety of expressions (but not too scary, please). You can also play pop-up by poking your head out around doorways and corners in the house.

Telephone Talk

It's clear when a baby's verbal skills are ramping up: She's constantly trying to communicate with you with an ever-growing store of sounds. Here's a playful way to help her keep working on that speech.

Skills developed: verbal
What you'll need: two play telephones, or real phones that are turned off or disconnected

Give your baby one telephone, holding the receiver up to her ear. Then use your telephone to hold a one-sided conversation, using a slow, exaggerated speaking style. Leave long pauses between your questions and comments, and soon you'll notice her beginning to make gurgling and cooing responses. This is a great way for you to help your baby practice the rhythms of conversation — sooner than you might think, she'll join in with her own two cents.

Shadow Show

Welcome to the watching age — when babies are transfixed by moving patterns and shapes. You may notice your little one staring at the TV now, whereas before he ignored it. Make him an active audience with an on-the-wall shape-making game.

Skills developed: visual
What you'll need: a flashlight

Many cultures have created forms of theater using shadows, and babies love both the spookiness and surprise of it. Sit on the floor with your baby in your lap or next to you. Position a flashlight so it shines against a wall, then put your hands in between the beam and the wall so that the wall serves as a screen. Start with simple activities like waving and holding up different numbers of fingers. Then use your hands to make animal shapes, such as a dog. Help your baby wave his hands to make simple shadows, and point out to him how much smaller his hand-shadows are than yours. Finally, hold his hands in yours and help him form the different shadow shapes, then have them say goodnight to him.

Source: www.babycenter.com

Appendix D: Activities for 6 month old TEDDY babies

Focus: Turn-taking games with sounds, repetitive sounds (sheep says Baa, Baa, dog says bow wow). Fuzzy or other interesting textures, soft balls or animals. Nesting cylinders, jingle bell toys.

My Photo Album

Recognizing familiar faces (including your own) is an enormous treat for your baby as he learns to identify people by name and association.

Skills developed: pattern recognition, fine motor
What you'll need: a small photo album — the type where the photos slide into clear plastic pockets

Buy a small photo album (one that holds 3-by-5- or 4-by-6-inch photos — one to a page is the best) and fill it with snapshots of your baby and the people in his life. In addition to relatives and family friends (the most typical photo subjects), make sure you include pictures of babysitters or caregivers, neighbors, and other babies and children you know.

Give the album to your baby and tell him it's his very own. Sit with him and show him the photos, letting him communicate his feelings to you. He'll react to the familiar ones with excitement and point out any faces he doesn't recognize with a questioning expression. Then put the album in his bookshelf or toy box, where he can page through it on his own. It'll quickly become a favorite — and a lifesaver on plane trips and long car rides.

Clap, Clap Your Hands

There comes a miraculous moment, sometime around the 6-month mark, when your baby discovers she can spontaneously bring her hands together to touch each other. But even before she masters this skill, clapping games give her a thrill. What's more, they provide a chance to interact with you face-to-face and to try to mimic your actions.

Skills developed: two-hand coordination
What you'll need: no equipment necessary

Patty-cake is an old favorite for babies, but this version is a little more challenging. Sit your baby on the floor, then sit down cross-legged facing her. If she doesn't sit securely yet, prop a pillow behind her. Then sing this song (any tune will do), acting out the commands as you come to them.

Clap, clap, clap your hands
Clap your tiny hands
Clap, clap, clap your hands
Clap your tiny hands

Additional verses:
Stomp, stomp, stomp your feet... (and so on).
Pat, pat, pat your head... (and so on).
Rub, rub, rub your tummy... (and so on).

Help your baby make the movements herself, even if it means holding her ankles and stomping her feet for her. You can continue to make up sillier and sillier verses (wiggle your eyebrows; stick out your tongue) as long as she continues to giggle.

Jack-in-the-Can

When a baby is getting the hang of object permanence (the idea that something still exists even when it can't be seen), any game where things appear and disappear is a hit. While traditional windup jack-in-the-boxes can still be too startling or scary at this age, you can make a baby-friendlier one yourself using simple materials from around the house.

Skills developed: understanding of object permanence
What you'll need: a coffee can, yogurt carton, or large paper cup; a chopstick, pencil, or ruler; a small colorful toy (a finger puppet works best); some tape or glue

Punch a hole in the bottom of the container. Insert a chopstick, pencil, or ruler (even a stick from your garden will do) through the hole, then glue or tape to the tip a small stuffed animal, plastic figure, or, even better, a finger puppet (just slip it over the end of the stick and secure it with a bit of tape). Now you have a hand-operated pop-up toy: Pull the stick down so the toy or puppet is hidden inside the can or cup, then push it up suddenly when you want the jack-in-the-can to greet your baby.

Watch What Happens

As babies become more observant and attuned to the notion of cause and effect, they become fascinated with light switches, TV remotes, and other things that seem like powerful agents of change. Cater to that fascination by showing your baby how certain actions bring certain results.

Skills developed: sense of cause and effect
What you'll need: no equipment necessary

Start with simple changes: Open and close a cupboard door or dresser drawer, then turn a light switch on and off (besides on/off, this demonstrates light versus dark). Then branch out into more active scenarios: Roll a ball across the floor to your baby or put a stuffed animal at the edge of the table, then push it off onto the chair. If you're feeling really adventurous, let her turn the faucet on and off — as long as it's the cold one.

Rodeo Days

Babies love surprises, and being surprised (and then learning to predict what might happen) is one way your baby learns that actions have consequences.

Skills developed: sense of cause and effect
What you'll need: no equipment necessary

Sit on a chair or sofa with your knees together and legs bent at a right angle. Sit your baby on your knees facing you with her legs to either side. Place your hands on your baby's waist to steady her and bounce her gently on your knees, saying, "This is the way the lady rides, tri-tree-tree-tree, tri-tree-tree-tree, this is the way the lady rides, tri-tree tri-tree tri-TREE." On the final "tree," part your legs so your baby dips dramatically down between them, taking care of course that she doesn't fall all the way to the floor.

The second and third verses have increasingly dramatic bouncing rhythms and falls: "This is the way the gentleman rides, gallop-a-trot, gallop-a-trot, this is the way the gentleman rides, gallop-a-gallop-a-TROT" — accompanied by a firmer bounce and a more pronounced dip — and then (the final verse), "This is the way the farmer rides, hobbledy-hoy, hobbledy-hoy, this is the way the farmer rides, hobbledy-hobbledy-HOY." Here, sway your knees from side to side, rocking your baby as if she were a farmer being carried on a swaybacked nag, and on the final "hoy," tip your baby sideways off your knees, catching her in your arms as she dips.

Bubble Bottle

Remember the hypnotic effect of watching a lava lamp? Here's a toy that will have the same impact with your baby, and you can make it yourself for pennies. It's sure to become a favorite, both in the bath and around the house.

Skills developed: dexterity, familiarity with colors
What you'll need: a clear plastic bottle (or several) with a tightly fitting screw-on lid; food color; dish soap

Fill a large, clear plastic bottle, such as a soda pop or water bottle, one third full of water. Add a few drops of dish soap or other liquid soap and a few drops of food coloring. Close the bottle tightly and give it to your baby; show him how to shake it up and make eye-catching colored bubbles. Make several bubble bottles using different shades of food coloring and use them to introduce your baby to the various colors. Show him how to roll the bottles across the floor.

Hide 'n' Eat

All kinds of hide-and-seek games are fun for your baby at this age, as he continues to be thrilled with the discovery that something hidden from him is still there after all. This variation on peekaboo livens up mealtime with the thrill of the chase.

Skills developed: fine motor, understanding of object permanence

What you'll need: a clean dish towel, finger foods, and some small opaque cups or containers

Show your baby a snack (anything that's not too wet or mushy), then cover it with a cloth dish towel or napkin. Let him lift the veil and discover that his treat is still there, even though he couldn't see it just a moment ago.

You can also inject a little sleight of hand: Put two cookies or slices of fruit in front of your baby, then cover them with opaque cups or other containers, adding at least one extra container that's not covering anything. Swirl the cups around so he can't tell which ones are hiding food, then let him lift off the cups and find his treats.

Appendix E: Activities for 9 month old TEDDY babies

Focus: Be aware of the beginnings of separation and stranger anxiety. Encourage including any favorite security items. Picture board books, nesting blocks, hand puppets, peek-a-boo.

Inside the Box

Now that she's got the motor skills to explore new territory, your baby is ready for some basic spatial concepts. A computer carton or other large box can introduce her to "inside" and "outside" — and also provides the perfect secret hideout.

Skills developed: gross motor, spatial relations
What you'll need: a sturdy cardboard box big enough for your baby to crawl in and out of

Put a soft blanket and some toys and books in the box with your baby and let her explore her own little space. Babies who are mobile can climb in and out of a box with 8-inch sides. A taller-sided carton provides more privacy, but watch carefully or she might tip it over. Cut windows out of a tall crate and you've created a "clubhouse," where your baby can play peekaboo with you and get her first deliciously powerful taste of "no parents allowed."

Safety note: Never leave your baby unattended in the box, as it could tip over.

Another option: Use a large appliance box turned on its side, and let your baby crawl in and out at her leisure.

Where Did It Go?

Your baby still delights in the surprise of finding something that was previously hidden, and his increasing fine motor skills allow for all sorts of new hunting and finding games.

Skills developed: fine motor, understanding of object permanence
What you'll need: a sandbox, a few small colorful objects (sticks or coins will do in a pinch)

At the park, the beach, or in a backyard sandbox, show your baby a brightly colored object (sunglasses, a plastic dinosaur, anything that will stand out reasonably well). With your baby watching you, bury it under a small mound of sand. With a perplexed look on your face, say, "Now where did those sunglasses go?" Then put your baby's hand on the mound of sand and help him brush the sand away until the object is uncovered. Once he gets the hang of the search, he'll do the digging without help. Gradually, you can move on to hiding the item when he's not watching.

Flour Power

You've probably already noticed that whatever you do, your baby wants to do the same thing.

Make a game of this mimicry by giving him a chance to "cook" — he'll enjoy playing grown-up and delight in the new textures you're introducing.

Skills developed: fine motor
What you'll need: newspaper, a flour sifter or measuring cup, and some flour or cornmeal

Spread some newspaper on the floor, then put a little pile of flour or corn meal on it and let your baby mix his own "cake." If you have a flour sifter, show him how to put the flour in and turn the handle. If you don't, a strainer is just as much fun. Together, use measuring spoons or a cup to scoop up the flour and dump it out again — he'll have a ball copying your moves. Pour a little on his hands or feet so he can explore the sensation of the flour on his skin. Things will get a bit messy, sure, but the scene will make for some classic photo opportunities.

Safety note: Don't leave your baby alone when he's playing with flour. It could interfere with his breathing if he were to inhale a big cloud or get a heaping handful in his mouth.

Squirt the Tummy

Reading books about body parts is fun, but why not play a game that teaches your baby to identify her own?

Skills developed: familiarity with body parts
What you'll need: a simple, gentle squirt gun or other squirt toy

With your baby seated in a warm bath — either in a swiveling bath seat, on a foam bath pad, or just in the tub watched closely by you — get out a squirt toy and fill it with warm bathwater. (For safety's sake, bring it with you to the tub; never leave a baby unattended to retrieve a toy.) Let your baby see the squirt toy and watch you fill it so there won't be too much surprise. Ask your baby, "Where's your tummy?" and then point to it with your finger and say, "There's your tummy!" Finally, squirt your baby's tummy gently, saying "I'm squirting your tummy!" Repeat for arms, legs, back, shoulders, and other body parts (never squirt your baby near the face — aim below the neck).

If your baby likes the surprise element here, drop the question-and-answer part and simply squirt each body part, saying, "I'm squirting your legs!" "I'm squirting your elbow!" and so on, varying the order so your giggly target never knows which body part will be next.

My Little Thumbkin

Fingers are fascinating to your baby because he's discovering how much they can do. In the classic children's singing game "Where Is Thumbkin?" the individual digits of each hand really come to life.

Skills developed: fine motor, auditory
What you'll need: a nonpermanent pen

Use a pen to draw a small face on the pad of each of your fingers and both thumbs. Start by making fists and holding them both out in front of your baby, clenched tight so no fingers show. To the tune of "Frère Jacques," sing:

"Where is Thumbkin, where is Thumbkin?"
"Here I am, here I am" (bring out one thumb, then the other),
"How are you today, sir?" (make one thumb bow),
"Very well, I thank you" (the other thumb returns the bow),
"Run away, run away" (put one hand, then the other, behind your back).

The song repeats with each finger called by name: Pointer, Tallman, Ringman, and Pinky. Then, for the grand finale, sing, "Where's the whole family?" waving all five fingers together on "Here we are." If you've given each finger-face a slightly different expression, this last verse is a hilarious hands-down winner.

Sticky Situation

When your baby has mastered the knack of picking up and manipulating toys, she's ready for the surprise silliness of this captivating challenge.

Skills developed: fine motor, hand-eye coordination
What you'll need: a piece of contact paper, tape, and a few small toys

Take a piece of sticky contact paper, the kind you use for lining drawers and shelves, and place it, sticky side up, on your kitchen floor. Then tape it down securely along all four edges. (You can put some newspaper down first for extra protection.) Gather an assortment of small toys and arrange them on the paper, pushing down on them to make sure they're firmly adhering. Then show your baby the toys and encourage her to pick them up — or try to. You'll both get a good laugh as your baby figures out how to get them un-stuck. Once all the toys are rescued, help her step barefoot onto the contact paper. She's likely to be fascinated with the sensation of the sticky surface pulling at her soles as you help her lift each foot and put it down again. Of course, if she doesn't like the sticky feeling, don't force the issue.

Classified Information

Sometime around 9 months comes the urge to categorize. But playing with plastic shape sorters has its limits if a baby hasn't mastered the spatial skill of fitting the shapes through the correct holes. This homemade alternative helps him sort things out on his own.

Skills developed: sorting, fine motor
What you'll need: a muffin tin, preferably one for 12 muffins, and groups of seashells or other objects

Collect a few large groups of related small objects such as seashells, rubber balls, or even large hair barrettes. Show your baby how to put an object into each cup of a muffin tin. Then,

after you've helped him fill the tin and dump it out a few times, sort the same types of objects into their own cups. This is a game you can continue to play for years, making it more sophisticated in terms of sorting and matching, grouping items, for example, by color and shape.

Safety note: Don't use any objects that are small enough for your baby to swallow.

Campfire Tales

Story hour is extra-special now that your baby seems to treasure particular picture books. Make it even more fun by turning it into a "campout." (It's a good way to get in some quiet cuddling time on a cold winter night or a long midsummer evening when darkness doesn't come early enough.).

Skills developed: verbal, pre-reading
What you'll need: a large sheet or blanket, two or three chairs, a flashlight, books

Position two kitchen chairs near a third piece of furniture, such as a table or sofa, or use three chairs, and stretch a large sheet or blanket over them to make a tent. (A cotton sheet is coolest on a hot night, a wooly blanket coziest on a cold one.) Use nonbreakable weighty objects like shoes or books to anchor the edges. Settle in together with some books and a favorite bedtime toy or blankie, and savor the joys of reading by flashlight.

Source: www.babycenter.com

A Great Fall

Nothing is as much fun as a game with a surprise ending. Combine that with rhythmic speech, which is easy for babies to follow, and you've got a winning combination.

Skills developed: gross motor, sense of cause and effect
What you'll need: no equipment necessary

On a rug indoors or outside on soft grass, lie on your back with your knees raised. Seat your baby on your tummy facing you, leaning back against your knees. Steadying her with your hands, sway from side to side. Start reciting the well-known nursery rhyme "Humpty Dumpty sat on a wall, Humpty Dumpty had a great..." and on the word "fall," tip your knees and roll to the side so that your baby slides off sideways onto the ground (use your hands to make sure it's a soft landing). Finish saying the rest of the rhyme curled up on the floor with your baby, ending with a quick tickle when you get to the phrase "together again." Then help her get situated on your tummy again for another go-round. You can add a further element of surprise by varying the point in the nursery rhyme when the fall occurs, so she doesn't see it coming.

Source: www.babycenter.com

Appendix F: Activities for 12 month old TEDDY babies

Focus: interesting board books, games with simple directions (hand me the ball). Placing objects into containers and dumping them out again. Pointing to body parts- where is your nose, where is your mouth, etc.

String-Along

Small round objects are extra-enticing now that your baby is mastering the "pincer grasp." Seize the chance to hone those fine motor skills while also (hopefully) getting her to sit still for a little more breakfast than usual.

Skills developed: fine motor, hand-eye coordination
What you'll need: sturdy string, plastic cord, or a shoelace; cereal-Os

On a highchair tray or nonbreakable plate, spread a thin layer of any kind of cereal-Os that have reasonably large holes. Cut a 20-inch piece of string or plastic cord (sold in craft stores), or use a thin shoelace with plastic-coated ends. Tie a knot in one end, or tie the cord around a cereal-O, to prevent the others from slipping off. Show your baby how to thread the cord through the cereal, then sit back and read the newspaper for a few minutes of uninterrupted peace.

Variation: As a special, occasional treat for an older child, this activity is a real thrill if the stringing is done with shoestring licorice and colorful cereal such as Froot Loops. Once she's finished, she can devour the entire necklace.

Package Play

We all like getting presents, but for babies, the unwrapping's the thing. There's both the thrill of discovery and the fun of making his fingers do what he wants. In this game, it doesn't seem to matter that the "present" is actually a bath toy he's been playing with for months — it's the element of surprise that counts.

Skills developed: hand-eye coordination, understanding of object permanence
What you'll need: a washcloth or two and some small plastic bath toys

With your baby seated in the bath, distract him for a moment and use a wet washcloth to "wrap" a small bath toy, such as a rubber duckie or plastic dinosaur. Present him with the "package," saying, "I'm giving you a present." He'll unfold the washcloth, squeal with delight, and immediately want to do it again. If you have two washcloths handy, you can start wrapping the next present while he's busy unwrapping the first one. As he gets older and his dexterity increases, he'll delight in wrapping such presents for you to open, a wonderful way to encourage his natural sense of generosity.

Food Faces

This game teaches your baby to construct a pattern (in this case a face) — and who would guess such fun is also a way to hone the fine motor skills needed for eating? It works best if your baby is either in a highchair, seated on your lap, or in a booster seat at the "big table."

Skills developed: pattern recognition, fine motor
What you'll need: a meal that includes several small, easily manipulated items such as peas, cubed cooked carrots, corn off the cob, cherry tomatoes cut in half, coarsely grated cheese, meat cut into small bits, noodles or spaghetti

Set out the different parts of your baby's meal in small, nonbreakable bowls: cooked peas in one bowl, cubed meat in another, and so on. Place a large, relatively flat plate (not a compartmentalized toddler plate) in front of your baby, and help her make a face out of her dinner. You'll need to be the art director here, but your baby can take handfuls of food and place them (more or less) where you say: "Put the cheese here for the hair... let's use a tomato for the nose." (Tip: Cooked carrot cubes are great for eyes, and spaghetti and other noodles make very convincing hair.) Guide her hands if necessary, and then do the final arranging yourself. When the face is done, you're ready to eat. Hopefully, though, your baby's been snacking the whole way through.

Safety note: Round objects pose a choking risk, so definitely cut those cherry tomatoes and grapes in half, and cook meat and peas and other vegetables until very soft.

My Little Trampoline

It's no secret that kids love to jump on beds. Actually, babies do too, and it's a perfect way for little ones to build lower-body strength and learn to control their wobbly legs.

Skills developed: standing, walking
What you'll need: a bed with a springy mattress

Stand your baby upright in the middle of your bed, carefully supporting him with your hands holding both sides. Help him bounce up and down, lifting him off the bed, then landing him in a standing position. If your baby is already walking, you may be able to just hold his hands, once he gets used to the springy motion of the bed.

Another fun game: Have him sit on the bed with his legs out in front of him and gently bounce the bed with your hands.

Safety note: Never leave a baby unattended on a bed.

Tube Tunnel

The pincer grasp — being able to hold a small object between the thumb and forefinger — is one of the fine motor milestones, and once your baby can do it, he'll want to do it all the time. This activity is perfect for babies who have learned to manipulate with their fingers.

Skills developed: fine motor, sense of cause and effect
What you'll need: one or more long cardboard tubes, such as those inside wrapping paper or paper towels; small balls such as golf balls

Sit on the floor with your baby, and show him how to hold the tube at an angle to the floor. Take a ball and show him as you put it in the top of the tube. Tell him to watch the bottom to see it roll out; he'll smile excitedly when it does. You can also rest the bottom of the tube on a large block or stack of books so it's easier to see the balls rolling out. Let your baby put the ball into the tube himself, and show him how to tilt the tube more or less to make the ball roll faster or slower.

Once he gets the hang of rolling the ball down the slide, you can play games such as marking where each ball finishes and seeing which ball rolls the longest distance. You can make the tube steeper and show your baby how the ball rolls faster and farther. Or you can keep the angle of the tube the same and try different types of balls, to see which ones go the farthest.

Variation: Cut a tube in half lengthwise to make a trough so your baby can see the ball as it's sliding down (as shown in the photo). Tape several of these troughs together in a zigzag pattern (cutting angled corners and taping them together with strong tape such as duct tape) to make a more dramatic ball course.

Little Home-Wrecker

Yes, it's goofy, but this game is a great way to help your baby build upper body strength. And ironically enough, considering the name, it's great for family bonding. It will get you laughing as loudly as your baby.

Skills developed: gross motor
What you'll need: two adults

Sit on the floor back to back with your spouse or another adult and challenge your baby to pry you apart. (If she's walking, she can do this standing up, but if she's crawling, doing it on hands and knees works fine.) To convey the concept to your baby, begin by sitting back-to-back with her and having the second adult squeeze in between the two of you. When it's your baby's turn, she'll have great fun trying to push and pull these huge, unwieldy adults. When she manages to make some room between you (you might have to help just a little), encourage her to insert herself in the middle, then lean back toward each other and gently "squish" her.

Diaper Dolly

A baby's penchant for "monkey see, monkey do" can add a cheery dimension to diaper changes — a fun first lesson in what it feels like to care for someone else.

Skills developed: fine motor, nurturing
What you'll need: a doll with easily removable clothes

Buy or make a doll with simple, removable clothes (preferably including a diaper) so your baby can change her dolly while you change her. (Of course, this will be easier for her when she's older, but even at this age she can remove a simple Velcro-ed diaper and possibly a shirt or dress, and what she can't get off you can take off for her.) Give her a square of toilet paper to wipe her doll's bottom while she's being cleaned up, and finally, your baby and her dolly can get dressed together and head back to play.

Water "Coloring"

The next time you need to get a little work done outside, try this simple activity. It will keep an older baby engrossed for a surprising amount of time — developing all the fine motor skills of painting (without the mess).

Skills developed: hand-eye coordination
What you'll need: some inexpensive paintbrushes and a bucket of water

Outdoors, fill a large bucket with water and give your baby several real paintbrushes (either bristle or foam is fine). Set him up so he's sitting in front of a wall or low piece of outdoor furniture, such as a step stool or bench, then show him how to "paint" it with water. Never mind if the water is going everywhere but on the piece to be painted; your baby will feel very proud that he's helping you get such an important job done.

Climb Every Cushion

Even as your baby learns to walk, she'll set her sights on climbing. You'll spend lots of extra minutes getting up your front steps and into the house because she'll want to scale the stairs all by herself — not once, not twice, but until you call off the ascent.

Skills developed: gross motor
What you'll need: lots of pillows from the bed, sofa, and elsewhere

Pile up a high stack of pillows for a safe, fun climbing activity. Use the largest, most stable pillows, such as couch cushions and bed pillows, on the bottom, then add chair pillows, throw pillows, and so on. Holding your baby steady, help her climb up the mountain of pillows and stand triumphant on top. If you have a lot of rectangular pillows, you can use them to create more of a stair-step structure, but you'll need to hold your baby's hand to make sure she doesn't step off the top tier into thin air.

Safety note: Never leave a baby alone with her pillow mountain; this activity should be supervised constantly. And move any furniture with sharp corners, so there's nothing for her to bang against if she falls.

Indoor Beach Baby

No time to get to the park? Not to worry: Here's a way your baby can do all the sifting, measuring, pouring, and fantasizing that comes with sandbox play.

Skills developed: fine motor, imagination
What you'll need: a dishpan or other large, relatively shallow container; cornmeal or sand; newspaper; and some sand toys or cooking utensils

Spread newspaper on the kitchen floor, then fill a dishpan or other shallow container with corn meal (or sand from an actual sandbox, if you have one) and place it on top. Offer some small sand toys or kitchen utensils to play with. Mini strainers, sifters, and flour scoops are great fun, as are measuring cups and spoons and, of course, good old buckets and shovels.

Appendix G: Finland's MOO instructions for distribution of the First Junior Scientist Information Packet and Parent Letter

The first Junior Scientist information package includes:

- Letter to parent
- Junior Scientist book
- Activity book
- Pin

The information package should be given to all TEDDY children. We give out the whole information package at the 5.5 year visit. For children older than 5.5, we give the package at the next occurring visit.

The nurse marks to her papers at which visit (visit and date) the package has been handed out. At the next visit the nurse should ask if the family read the book. The nurse should mark when she asked (visit and date) and the answer (YES, NO).

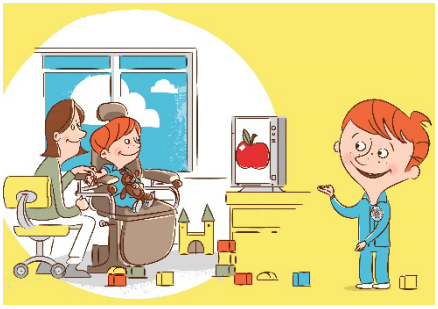
Once the DCC develops a way to track these events, the nurses will transfer the data from their papers to the database.

For children on Long Distance Protocol, the information package is sent by mail. The answer whether the book was read or not is asked at the next phone interview.

Kirje TEDDY-tutkimuslasten vanhemmille

Hyvät vanhemmat, olemme kiitollisia perheenne osallistumisesta TEDDY-tutkimukseen. Toivomme, että tiedätte, kuinka tärkeää meille on osallistumisenne tällaiseen pitkäaikaiseen tutkimukseen.

Perheenne on ollut mukana TEDDY-tutkimuksessa jo jonkin aikaa. Kun lapsenne oli vauva, te teitte kaikki TEDDY-tutkimukseen liittyvät asiat. Nyt kun lapsenne on kasvanut isommaksi, hän voi itse osallistua enemmän TEDDY-asioihin tutkimuskäynneillä ja kotona. Haluamme auttaa tekemään sen helpommaksi teille ja lapsellenne.



Auttaaksemme lastanne ymmärtämään ja tuntemaan olevansa osa TEDDY-tutkimusta, olemme tehneet kirjasarjan nimeltä : ”Ville ja Emma – Pikku-Tutkijat”. Ensimmäinen kirja on tarkoitettu 6-7-vuotiaille lapsille. Kirjassa kerrotaan TEDDY-tutkimuksesta hauskalla tavalla. Pikku-Tutkijat paketti sisältää myös puuhakirjan ja rintamerkin.

Toivomme, että luette kirjan yhdessä lapsenne kanssa. Kirjan lopussa on muutamia tärkeitä kysymyksiä lapselle ja niistä keskustelemalla huomaatte, ymmärtääkö hän TEDDY-tutkimuksen tarkoituksen. Haluamme rohkaista teitä lukemaan kirjan useita kertoja lapsenne kanssa tutkimuskäyntien välissä, jotta hän ymmärtäisi ja muistaisi paremmin tutkimuksen tarkoitukset.

Seuraava kirja tarjoaa lisää tietoa TEDDY-tutkimuksesta, myös hauskalla ja jännittävällä tavalla.

Toivomme, että kerrotte, jos teillä vanhemmilla on muita ajatuksia, miten voisimme auttaa teitä jatkamaan edelleen TEDDY-tutkimuksessa. Olemme kiitollisia kaikista ideoista.

Suurkiitos vielä kerran koko perheellenne!

Terveisin,
TEDDY-tutkimuksen väki

Appendix H: Sweden's MOO instructions for distribution of the First Junior Scientist Information Packet and Parent Letter

The first Junior Scientist information package includes:

- Letter to parent
- Junior Scientist book
- Activity book
- Pin

The information package should be given to all TEDDY children. We give out the whole information package at the 5.5 year visit. For children older than 5.5, we give the package at the next occurring visit.

The nurse marks to her checklist at which visit (visit and date) the package has been handed out. At the next visit the nurse should ask if the family read the book. The nurse should mark when she asked (visit and date) and the answer (YES, NO).

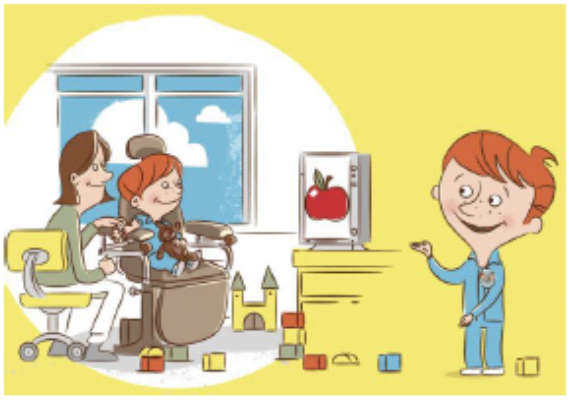
Once the DCC develops a way to track these events, the nurses will transfer the data from their papers to the database.

For children on Long Distance Protocol, the information package is sent by mail. The answer whether the book was read or not is asked at the next phone interview.

KÄRA TEDDY-FÖRÄLDER

Ni har nu deltagit i TEDDY-studien under en längre tid och vi har försökt utveckla olika sätt för att ni och ert barn skall känna er delaktiga i studien. Mycket av detta har inneburit att ni föräldrar fått information om TEDDY och dess olika delar, medan våra ansträngningar vad gäller barnet ofta har handlat om att barnet ska känna trygghet i att komma på TEDDY-besöken.

Eftersom ert TEDDY-barn nu är äldre innebär det att barnet kan förstå mer om TEDDY och på ett annat sätt kan bli delaktigt i studien. Både svenska och internationella riktlinjer säger att forskare är skyldiga att ge information även till barnen, när de har uppnått en ålder då de kan förstå mer komplicerade sammanhang. Samma riktlinjer säger också att barnen själva, när de blivit lite äldre, ska få möjlighet att ge sitt medgivande om att de vill delta i studien - från cirka 12 års ålder.



För att hjälpa barnen att förstå mer om TEDDY-studien och att förbereda dem för deras framtida samtycke till att vara med, har vi planerat en serie med böcker som utgår från den första Wille-boken, som barnet fick vid 2 år. Vi har förstått att många av TEDDY-barnen har uppskattat den boken.

Den andra boken, som ni nu får, är för barn från 5-6 år. Boken vill förklara för barnen vad TEDDY-studien går ut på och vad barnens deltagande innebär för både dem och för studien. Boken beskriver TEDDY-studiens mål och metoder och hur viktigt deras deltagande är för studien. Vi har också gjort en aktivitetsbok, som barnen kan sysselsätta sig med och en pin, som bevis på att de är en Miniforskare!

Vi ber att ni föräldrar i lugn och ro läser boken tillsammans med barnet. I slutet av boken har vi lagt till några frågor som ni kan ställa till barnet när ni läst boken. Syftet med frågorna är att försöka se till att ert barn har förstått vad boken vill berätta: varför just han/hon är med i TEDDY, lämnar prover och svarar på frågor och därför också är en Mini-forskare!

Om ni tycker att barnet inte riktigt kan svara på frågorna, så läs gärna boken en gång till. Prata om boken och ställ frågorna så att både ni och vi kan hjälpa barnet förstå hur viktigt det är för forskningen om autoimmun diabetes.

Tack än en gång för att er familj deltar i TEDDY-studien och hjälper oss att ta reda på varför barn får autoantikroppar mot sina betaceller och varför de sedan kan utveckla autoimmun (typ 1) diabetes.

Hälsningar från all personal i TEDDY-studien.

Appendix I: Georgia/Florida's MOO instructions for distribution of the First Junior Scientist Information Packet and Parent Letter

The first round of Jr. Scientist items includes:

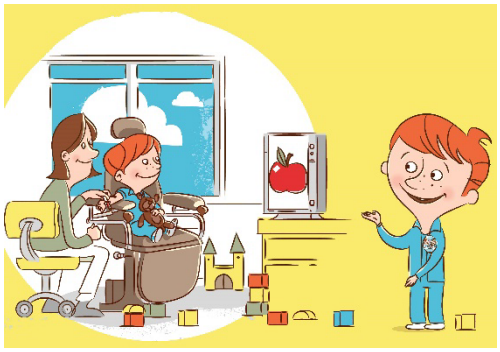
- Letter to parents introducing Jr. Scientist idea
- First Jr. Scientist story book
- Jr. Scientist activity book
- Jr. Scientist pin

GA/FL will to give out the letter to the parents, the first story book, and the activity book at the 6.5 year visit for all TEDDY children. If the visit is conducted in person, the items will be given out at the visit with an introduction/explanation. If the visit is not done in person (an LDP) then the materials will be mailed and discussed with the family via LDP methods (telephone, Skype, etc.). Staff will instruct/encourage the family to read the book together before the next visit, as GA/FL is required by both IRBs to assent the child at the age of 7. Staff will document locally that the materials have been given out, both in the chart via visit notes and electronically (temporary Excel spreadsheet) to assist the DCC is backfilling the data once their programming is in place.

At the 7 year old visit (or the next visit where assent is obtained) staff will confirm that materials were handed out, then will ask the parent/guardian if they read the book with the child, documenting their yes/no answer through the same methods listed above (in the chart and electronically). As the assent is discussed and signed, the child will receive the Jr. Scientist pin to signify their decision to continue as a voluntary research participant.

If key visits are missed, or if children have already passed these visits, staff will give out items when they next see or interact with the children.

Dear TEDDY Parent:
Thank you for your family's participation in the TEDDY study. We understand the commitment it takes to be part of a long-term study like TEDDY. We hope you know that your ongoing help is appreciated.
Your family has been in TEDDY for some time. When your child was a baby, you did much of the TEDDY work on your own. Now, your child has grown older and can become more involved in the TEDDY visits and tasks. We want to help make this change easier for you and your child.
One part of recognizing that your child is getting older is getting his or her assent or agreement to participate in TEDDY. National and international guidelines to protect children in research require that we get assent when your child turns 7 years old.
To help your child understand and feel more a part of TEDDY, we have created a series of books called "Will & Emma: The Junior Scientists." The first book is for children 6-7 years old. The book explains TEDDY to your child in a fun way.
The book explains the basics of the TEDDY study and describes TEDDY children as "TEDDY Junior Scientists," helping with very important research. We also have an activity book and a pin to give your child - a Junior Scientist "badge."
Please read the book together with your child at home. There are a few questions at the end of the book. Reading the book together and discussing the questions with your child will help you know if your child understands the purpose of the study and why he or she is participating in TEDDY.



The next book will provide some more in-depth facts about the TEDDY study, also in a fun and exciting way.
If there are other ways we can aid you in being involved in the TEDDY study, please let us know. We are grateful for all ideas.
Thank you again for being a part of TEDDY!
Sincerely,

Leigh Steed
Study Coordinator

J. Germany's MOO instructions for distribution of the First Junior Scientist Information Packet and Parent Letter

The first Junior Scientist information package includes:

- Letter to parent
- Junior Scientist book
- Activity book
- "Junior Scientist" Pin

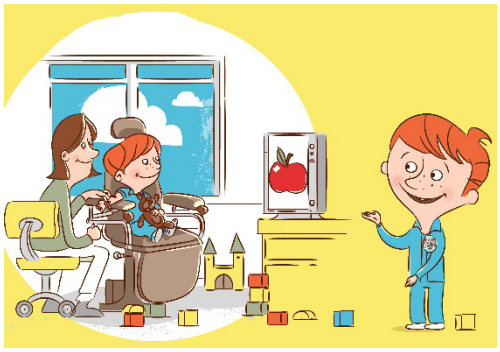
The information package will be given to all TEDDY children starting at age 5.5/ 6 years of age to the oldest TEDDY children. We give out the complete information package at the upcoming visit.

Long distance protocol:
For families on long distance protocol parents will be informed about the Junior Scientist package and the purpose of the information package by phone. Furthermore parents are asked to read the book together with their child, preferably several times (as indicated in the parent letter). Then the Junior Scientist package will be sent out by post to the families together with the next visit material distribution. Hand out of the material is recorded in a staff shared excel list. The study nurse will mark when she handed out material (visit and date).

At the next scheduled phone call the nurse will ask the family if they have read the book and note this information in the staff shared excel file (YES, NO).

Visits at clinical site:
The nurse notes in the staff shared excel list at which visit (visit and date) the package has been handed out. At the next visit the nurse will ask if the family has read the book. The nurse will record the answer in the list (YES or NO).

Liebe TEDDY Eltern,
vielen Dank, dass Sie und Ihre Familie an der TEDDY Studie teilnehmen. Ihr Engagement für diese Langzeitstudie wissen wir sehr zu schätzen und Ihre weiter währende Unterstützung mit Ihrer Teilnahme ist für uns sehr wichtig!
Bereits seit längerer Zeit nehmen Sie und Ihre Familie an der TEDDY-Studie teil. Als Ihr Kind noch ein Baby war, haben Sie viele TEDDY Aufgaben selbst erledigt. Nachdem Ihr Kind nun älter geworden ist, kann es nun mehr in die TEDDY Untersuchungen und „Hausaufgaben“ eingebunden werden. Und dabei möchten wir Ihnen helfen.
Nationale und internationale Richtlinien zum Schutze von Kindern in der Forschung unterstützen, dass wir Ihr Kind über die Teilnahme an der TEDDY Studie informieren.
Damit Ihr Kind nachvollziehen kann, um was es bei der TEDDY Studie geht, und sich mehr als Teil der TEDDY Studie verstehen kann, haben wir eine Bücherreihe mit dem Titel „Emil & Emma: Kleiner Forscher” zusammengestellt. Das erste Buch wurde für Kinder im Alter von 6 bis 7 Jahren konzipiert. Auf eine unterhaltsame Weise erklärt es Ihrem Kind die TEDDY Studie.
Das Buch geht auf die wichtigsten Punkte der TEDDY Studie ein und illustriert, wie Kinder, indem sie als „Kleine TEDDY Forscher” teilnehmen, einen wichtigen Beitrag zur Forschung leisten. Begleitend dazu gibt es ein Spiel- und Malbuch und einen „Kleiner Forscher“ Anstecker, den Sie Ihrem Kind geben können.



Bitte lesen Sie gemeinsam mit Ihrem Kind daheim dieses Buch durch. Wir würden es sogar begrüßen, wenn Sie dieses Buch mit Ihrem Kind mehrmals zwischen den Untersuchungen lesen, damit es die Gedanken dieses Buches besser verstehen und merken kann. Am Ende des Buches finden Sie einige leichte Fragen. Wir würden uns freuen, wenn Sie diese Fragen mit Ihrem Kind besprechen würden, um sicher zu gehen, dass es die TEDDY Studie verstanden hat und weiß, was es bedeutet, an der TEDDY Studie teilzunehmen.
Das nächste Buch wird – in einer genauso unterhaltsamen und spannenden Weise – tiefere Einblicke in die TEDDY Studie verleihen.
Sollten Ihnen noch andere Möglichkeiten einfallen, wie wir Ihnen als Eltern helfen können, lassen Sie es uns bitte wissen. Für jegliche Art von Vorschlägen sind wir Ihnen sehr dankbar.
Nochmals herzlichen Dank, dass Sie und Ihr Kind an der TEDDY Studie teilnehmen.
Mit freundlichen Grüßen
Ihr TEDDY Team

K. Washington's MOO instructions for distribution of the First Junior Scientist Information Packet

Items:

Letter to Parent
Junior Scientist Book
Activity Book
Junior Scientist Pin

Note: Schedule below if for both subjects on quarterly and semi-annual protocols.

In Person Visits:

6 Year Visit

Letter to Parent
Junior Scientist Book
(Parents should be instructed to read and review the book with the child prior to the 6.5 year visit)
Note the book was given out using TEDDY Tools from the main Call List

Click on TEDDY Tools
At initial prompt click "Jr Scientist"
This will create a log entry

Put the visit number and items given in the notes

6.5 Year Visit

Activity Book
(Parents should be asked if they read the book with the child)
Note the book given and parents response using TEDDY Tools

Click on TEDDY Tools
At initial prompt click "Jr Scientist"
This will create a log entry

Put the visit number, items given and parent's response in the notes

7 Year Visit

Junior Scientist Pin
(At the 7 year visit the child will undergo the regular verbal assent process. They should receive a certificate and Junior Scientist Pin at the end of the assent.)
Note the assent done and pin given using TEDDY Tools

Click on TEDDY Tools
At initial prompt click "Jr Scientist"
This will create a log entry

Put the visit number, items given and assent completed

Long Distance Protocol:

6 Year Birthday Card (items to be mailed home with card)

Letter to Parent

Junior Scientist Book

(Parents should be instructed to read and review the book with the child prior to the 6.5 year visit)

Note the book was mailed using TEDDY Tools from the main Call List

Click on TEDDY Tools

At initial prompt click "Jr Scientist"

This will create a log entry

Put the visit number and items given in the notes

6.5 Year Visit Packet

Activity Book (can be mailed separately)

(During scheduling call ask parents if they read the book with the child)

Note the book mailed and parents response using TEDDY Tools

Click on TEDDY Tools

At initial prompt click "Jr Scientist"

This will create a log entry

Put the visit number, items given and parent's response in the notes

7 Year Assent

Junior Scientist Pin (to be mailed after phone/Skype call)

(At the 7 year visit the child will undergo the regular verbal assent process. They should receive a certificate and Junior Scientist Pin at the end of the assent.)

Note the assent done and pin mailed using TEDDY Tools

Click on TEDDY Tools

At initial prompt click "Jr Scientist"

This will create a log entry

Put the visit number, items given and assent completed

Missed Visits:

6 Year Visit Missed

6 .5 Year Visit

Letter to Parent
Junior Scientist Book
(Parents should be instructed to read and review the book with the child prior to the 7 year visit)
Note the book was given out using TEDDY Tools from the main Call List
Click on TEDDY Tools
At initial prompt click "Jr Scientist"
This will create a log entry
Put the visit number and items given in the notes

7 Year Visit

Activity Book
(Parents should be asked if they read the book with the child)
Junior Scientist Pin
(At the 7 year visit the child will undergo the regular verbal assent process. They should receive a certificate and Junior Scientist Pin at the end of the assent.)
Note the assent done, book and pin given using TEDDY Tools
Click on TEDDY Tools
At initial prompt click "Jr Scientist"
This will create a log entry
Put the visit number, items given and assent completed

6.5 Year Visit Missed

6 Year Visit

Letter to Parent
Junior Scientist Book
(Parents should be instructed to read and review the book with the child prior to the 6.5 year visit)
Note the book was given out using TEDDY Tools from the main Call List
Click on TEDDY Tools
At initial prompt click "Jr Scientist"
This will create a log entry
Put the visit number and items given in the notes

7 Year Visit

Activity Book
(Parents should be asked if they read the book with the child)
Junior Scientist Pin
(At the 7 year visit the child will undergo the regular verbal assent process. They should receive a certificate and Junior Scientist Pin at the end of the assent.)
Note the assent done, book and pin given using TEDDY Tools
Click on TEDDY Tools
At initial prompt click "Jr Scientist"

This will create a log entry
Put the visit number, items given and assent completed

6 & 6.5 Year Visit Missed

7 Year Visit

Letter to Parent
Junior Scientist Book
(Parents should be instructed to read and review the book with the child prior to the 7.5 year visit)
Activity Book
Junior Scientist Pin
(At the 7 year visit the child will undergo the regular verbal assent process. They should receive a certificate and Junior Scientist Pin at the end of the assent.)
Note the assent done, book and pin given using TEDDY Tools
Click on TEDDY Tools
At initial prompt click "Jr Scientist"
This will create a log entry
Put the visit number, items given and assent completed

7.5 Year Visit

Ask parents if they read the book with the child
Note the parent's response using TEDDY Tools
Click on TEDDY Tools
At initial prompt click "Jr Scientist"
This will create a log entry
Put the visit number and parent's response

For Children already past the 7 year visit

At Next Clinic Visit

Letter to Parent
Junior Scientist Book
(Parents should be instructed to read and review the book with the child)
Activity Book
Junior Scientist Pin
Note the book and pin given using TEDDY Tools
Click on TEDDY Tools
At initial prompt click "Jr Scientist"
This will create a log entry
Put the visit number and items given

L. Colorado's MOO instructions for distribution of the First Junior Scientist Information Packet

Items:

Letter to Parent
Junior Scientist Book
Activity Book
Junior Scientist Pin

Clinic Visits:

6.5 Year Visit

Give Letter to Parent, Junior Scientist Book and Activity Book.
Clinic staff will use a script to explain the purpose of the book to the child and parent.
Parents will be instructed to read and review the book with the child prior to the 7 year visit.
Select "yes" for Junior Scientist Book in the local database under that clinic visit.

7 Year Visit

Ask parent if they read the Junior Scientist book and record yes/no answer in local database for that visit.
At the 7 year visit the child will undergo the verbal assent process. The Junior Scientist Pin will be given at the completion of the verbal assent.
*If either visit is missed the above protocol will be followed at the next visit.

Long Distance Visits:

6.5 Year Visit

Mail Letter to Parent, Junior Scientist Book and Activity Book.
Clinic staff will use a script to explain the purpose of the book to the child and parent.
Parents will be instructed to read and review the book with the child prior to the 7 year visit.
Select "yes" for Junior Scientist Book in the local database under that clinic visit.

7 Year Visit

Mail Junior Scientist Pin with 7 year visit packet.
Ask parent if they read the Junior Scientist book and record yes/no answer in local database for that visit.
At the 7 year visit the child will undergo the verbal assent process over the phone.
*If either visit is missed the above protocol will be followed at the next visit.

10. TEDDY Interviews and Questionnaires

10.1. Background and Rationale

Children with increased genetic risk will be followed to assess environmental exposures with a clinic visit every 3 months for the first 4 years of life. At 4 years of age and beyond those children who have been deemed persistent autoantibody positive will follow a 3 month visit schedule (confirmation results from the confirmatory Autoantibody lab will not be taken into consideration for determining the subject's visit schedule, only the local lab's results will be used for this); all other subjects will attend biannual clinic visits beginning at 4 years of age until age 15. For subjects who become autoantibody positive at 4 years of age or older, the subject will be reinstated on the 3 month visit schedule at the first indication of autoantibody positivity and will stay on if persistent. If the next available sample is negative, thus the subject is not deemed persistent autoantibody positive, the subject will be seen every 6 months instead of every 3 months from that point on. Subjects who have been persistently single autoantibody positive, but who become negative to all antibodies for 1 year or more will be placed on the biannual visit schedule after 4 years of age. Subjects who have been persistently multiple autoantibody positive, but who become negative to all antibodies for 1 year or more will remain on the three month visit schedule. The exposures of primary interest include: in-utero exposures during pregnancy, timing of introduction and/or type of dietary constituents, intake of particular vitamins and minerals affecting immune system development, frequency and type of infections (viral and bacterial), timing and type of childhood immunizations, exposure to pets and allergy experience, weight gain, and experience of psychological stress. The TEDDY clinic visit schedule has been set at 4 times a year in the first 4 years of life for all subjects in order to assess these exposures close to when they actually happen and identify the appearance of the primary and secondary outcomes—the development of autoantibodies and T1D as close to onset as possible. This design attempts to minimize recall bias and provides the opportunity to place exposure and outcome on the proper time sequence relative to each other. The first four years of life are considered the critical time period in which to observe these exposures.

The TEDDY questionnaires and interviews are one of several methods used to assess these exposures and are critical components of the protocol. Other assessment methods include a series of 3-day-food diaries and one 24-hour recall protocol, the parent's TEDDY Book recording/extraction protocol, water sample collection, toenail sample collection, salivary cortisol sample collection and frequent stool, nasal and blood sample collection from the child. These are described separately in other sections of this manual of operations.

In addition to providing important information on environmental exposures, the TEDDY questionnaires and interviews provide important information about the impact of the protocol on the parent and the parent's perceptions of the child's risk for TID, parental emotional and behavioral reactions to the child's increased risk and parental satisfaction with the study protocol. The questionnaires and interviews

are also used to collect demographic and descriptive data about the child and family.

The questionnaire and interview data address three study goals. First, these data provide important environmental exposure information, contributing to the primary objective of the study. Second, these data will be used to document the impact of the study protocol on the participants. Third, the data will be used to identify the characteristics of families who stay in difficult longitudinal protocols of this type as well as the characteristics of families who drop out. This information will help us design more efficient natural history or intervention studies in the future.

10.2. Overview of Interviews/Questionnaires and Definition of Respondent

The interviews and most of the questionnaires are directed at the child's primary caretaker. In most cases, the primary caretaker will be the child's mother. However, if the child does not live with his/her mother, the person who is the child's primary caretaker should be interviewed and complete the questionnaires. In some cases this primary caretaker will be the father, a relative or someone unrelated to the child. Defining who should be the respondent in such cases should be based on the person who can best report the infant's daily life and who has knowledge of the kinds of exposures being assessed. Some of the questionnaires are designed to specifically capture fathers' opinions and perceptions about risk of T1D as well.

- First TEDDY Study Questionnaire for Mother, Father, Primary Caretaker
    - Depending upon the child's family structure the following First Questionnaires are to be obtained:
        - Mother and Father both present- Mother and Father Questionnaires.
        - Mother only present: Mother Questionnaire; inquire as to father's availability. If the father has regular contact with the child and the mother would like him to participate, the mother may invite him to complete the Father Questionnaire.
        - Father only present: Primary Caretaker Questionnaire.
        - Primary Caretaker other than parent: Primary Caretaker Questionnaire; inquire as to availability of mother or father. If either parent has regular contact with the child and the primary caretaker (assuming the primary caretaker is the child's legal guardian) wants him or her to participate, the primary caretaker may invite the mother or father to complete the Mother or Father Questionnaire.
- Primary Caretaker 3 Month Interview
- 6 Month Questionnaire for Mother, Father, or Primary Caretaker
- Family History Questionnaire
- Primary Caretaker 9 Month Interview
- Update form for Primary Caretaker Interview (data originally collected in the 9 month Primary Caretaker Interview Form)

- Annual Questionnaire for Mother, Father, or Primary Caretaker at 15, 27, 39, 48 month visits and annually thereafter through the 14 year visit. At the 15 year visit the End of TEDDY Parent Questionnaire will be administered.
- Child Behavior Checklist completed by one of the child's parents (or primary caretaker) when the child is 3.5, 4.5 and 5.5 years of age

Details about each questionnaire and interview are provided in Section 10.4

10.3. Administration, Review, and Coding

10.3.1 General Administrative Procedures

Administration details specific to each interview and questionnaire are described starting in section 10.4. This section reviews general administration procedures.

10.3.2 Procedures for self-administered questionnaires:

- An Instruction Sheet should be included with all questionnaires.
- For all questionnaires to be filled out at home, provide the toll free phone number to call study staff if the respondent has questions on the Instruction Sheet
- If possible, a black ink pen for completing the questionnaire should be provided.

10.3.3 Review of all self-administered questionnaires

It is important to review all self-administered questionnaires during the clinic visit in order to assure:

- The questionnaire is completed in black pen
- Any questions the respondent may have are answered
- The date the form was completed by the respondent
- No items are accidentally skipped
- If a respondent purposefully refuses an item, the reviewer will so note on the questionnaire and initial and date
- The respondent's answer is clear if a response to an item has been changed. If an answer is changed:
  - a large X should be drawn across the incorrect response, the respondent should initial and date next to it and the new answer should be clearly indicated
- The respondent has not filled in boxes designed for staff coding.
- All dates are written using the European format (day/month/year)

10.3.4 Administration of the 3-month interview, 9-month Interview and Update form for Primary Caretaker Interview (data originally collected in the 9 month Primary Caretaker Interview Form)

The 3-month interview is done at the child's first clinic visit with the primary caretaker, the 9-month interview is done at the child's 9 month

clinic visit with the primary caretaker, the update form for primary caretaker interview is done at the child's 21 month, 33 month, 45 month, 54 month, 6.5 year clinic visits and every two years thereafter.

- A black ink pen for completing the interview should be used by the clinical staff. Clarity of corrections needs to be a priority.
- Most answers require filling in a circle. Some answers require letters or numbers placed in boxes, staff should follow the same instructions given to parents.
- If an answer is changed, a large X should be drawn across the incorrect response, the staff member making the correction should initial and date next to it and the new answer should be clearly indicated.
- Dates use the European format: day/month/year.
- If a respondent purposefully refuses a question the interviewer should so note on the interview response form, initial and date.

10.3.5 Information to be completed by study staff

On each questionnaire or interview, staff should complete all information asked for in the "Office Use Only Box" located on either the first page (for interviews) and on the last page (for self-administered questionnaires):

- "Visit Location Code" this is the location where the TEDDY visit took place. Drop-down list based upon TEDDY Clinical Center field.
- "Date form was reviewed" in day/month/year format (see "Date form was Reviewed" on forms that are to be filled out by the parent/primary caretaker) this is the date that the form is reviewed by the study staff member with the parent/primary caretaker or "Interview Date" in day/month/year format (you will see "Interview Date" on forms that are completed through an interview) this is the date the interview took place.
- "Name of person reviewing the form" this is on forms that are to be filled out by the parent/primary caretaker; this is the person who goes over the answers on the form with the parent/primary caretaker or "Interviewer" you will see this on forms that are completed through an interview; this is the person who conducts the interview with the parent/primary caretaker, the code can be found in the member directory on the TEDDY website
- "TEDDY Staff Code of Person Reviewing Form" this is on forms that are to be filled out by the parent/primary caretaker; this is the person who goes over the answers on the form with the parent/primary caretaker or "TEDDY Staff Code of Interviewer" you will see this on forms that are completed through an interview; this is the person who conducts the interview with the parent/primary caretaker, the code can be found in the member directory on the TEDDY website.
- "Visit" this is on forms that are completed at different visits, so that you can indicate the visit that the particular form was completed at
- "Person(s) Interviewed" this is on forms that are completed through an interview; this is the parent/primary caretaker who the information was obtained from

10.3.6 Coding of participant responses

Certain question responses will require coding by study staff.

- Boxes for staff to code the respondent's answers are on the form; these codes are indicated by white boxes placed in a grey background.
- To keep clinic visits as efficient as possible, coding of questionnaire and interview responses will usually take place after the clinic visit.
- Every staff member doing coding will either 1) look up the code via the online TEDDY Code Book link which can be found under the section on the left navigational toolbar of the TEDDY website entitled "Study Management" or 2) maintain an up-to-date TEDDY Coding Notebook. This notebook will be divided by interview/questionnaire and each section will have the relevant question codes for that interview. Some codes will be used across instruments and these will be repeated as necessary.
- Study staff should be very familiar with the TEDDY codes so they are able to gather all necessary information from study participants to code responses correctly.
- If necessary, study staff may call the participants to gather clarifying information to permit accurate coding of all responses.
- Code boxes for ICD-10 codes consist of 3 digits, one decimal place, 1 digit, code boxes for medication codes consist of 8 digits, and all other codes consist of 5 digits. All code boxes are white boxes inset in gray areas and marked "Code".
- In cases where a staff person encounters a response that does not appear to have an appropriate code, the DCC needs to be queried.
- The DCC will be responsible for notifying all centers of additions to the question codes.
- Coding should be completed before data are sent to the DCC.

10.3.6.1 What to do when a code has not been assigned for a particular item

When a code has not been assigned for an item, email the DCC at teddy@epi.usf.edu. In the email provide the name of the item to be coded as well as the coding category (Reasons for Changing Baby's Formula, Types of Day Care, Types of Social Group, etc). The DCC will assign the item a code. If the item to be coded is questionable, the DCC will contact the appropriate person/committee to review the item.

If a proposed code item must be sent for review the clinical center staff member should use the 99999 (or 99999999 for medication codes or 999.9 for ICD-10 codes) code in the code box (codes that do not need to be reviewed will be assigned codes immediately). Once a decision has been made, and if a code is assigned, the clinical

center staff member will have to go to the online version of the form and enter the new code.

10.3.6.2 Announcement of Code Book changes

Each clinical center will designate a person at their site to be the 'code book contact person'. When a change has been made to the TEDDY code book, this person will be notified and it is his/her responsibility to notify the appropriate people at his/her site about this change. If applicable, the DCC will also contact the person who initiated the coding process of this particular item. Newly coded items will also be listed by default on the 'TEDDY Code Book' search page on the TEDDY website.

10.3.7 Conversion Table for Converting Age of Baby

The following conversion table will be used to convert the age of the baby as reported by the mother to what is asked for on the questionnaire.

Days 0-3 = 0 weeks = 0 months
Days 4-10 = 1 week = 0.25 month
Days 11-17 = 2 weeks = 0.50 month
Days 18-24 = 3 weeks = 0.75 month
Days 25-31 = 4 weeks = 1 month
Days 32-38 = 5 weeks = 1.25 months etc...

10.3.8 Participant distress and referral

Since study staff will be following families for long periods of time, rapport-building is encouraged. There may be occasions when family members express significant distress over some aspect of the study (e.g., learning the child is at increased risk for TID, a positive autoantibody result) or some other aspect of their life (e.g. divorce, death of a loved one). On the Six Month Questionnaire, postpartum depression is assessed and critical item and total score cut-offs are used to identify participants in need of assistance. However, there may be other occasions when the participant staff expresses significant distress and staff should provide and appropriate referral. Each site will specify its procedures for referral. All referrals should be noted on the Physical Exam form.

Because study staff may know intimate details about the family, other issues may come to the attention of the study staff (e.g., child abuse, neglect, spouse abuse, alcoholism). Study staff will follow reporting laws of their jurisdiction and make referrals for services as needed.

10.4 Detailed Questionnaire/Interview Administration, Review and Coding Instructions

10.4.1 Instruction Sheet

An Instruction Sheet and black pen should be provided with each questionnaire. The Instruction sheet is also useful for interviewers completing the interview response form. The Instruction Sheet tells the respondent to:

- Use a black ink pen
- The correct format for writing dates (**DD/MMM/YYYY)**
- Fill in circles completely using the black pen provided
- Enter numerical or alphabetical answers in the boxes provided, one letter or number to a box, leaving space between the number or letter and the side of the box
- Correct mistakes or change answers by drawing a large X over the incorrect response, initial and date next to it and to clearly indicate the new answer
- Ignore white boxes placed in a grey background with the words "Code (office use only)"

10.4.2 The First Questionnaire-Mother

This questionnaire is designed to be sent home before the child's first study visit and completed by the child's biological mother. The primary focus of this questionnaire is on the mother's pregnancy.

10.4.2.1 Content of the First Questionnaire-Mother

Questions generally ask about the mother's experience over the entire pregnancy. In some cases respondents are asked to note their experiences in different trimesters or in the last month of the pregnancy. This questionnaire is designed to be self-administered and provides detailed information on:

- The mother's health during her pregnancy (common illnesses and conditions including infections)
- Difficulties experienced during labor and delivery
- Experience of gestational diabetes and presence of type 1 or type 2 diabetes and treatment before, during and after pregnancy
- Evidence of maternal Rh Negative blood type and any treatment received
- Vaccines and medications (all types of prescription medications – oral, topical, injection, etc – but only oral non-prescription medication) taken during her pregnancy
    - If the mother takes a pure homeopathic preparation during pregnancy and it is being given to alleviate symptoms associated with a condition that can be defined by an ICD-10 code, the name of the homeopathic (if known) along with indication that it is a homeopathic preparation should be written under "name of medication". Sites should review the complete ingredient list of the product before classifying it as purely homeopathic. If the product

contains added vitamins, minerals probiotics, etc then it should be coded in the dietary supplements section. If the product is deemed to be purely homeopathic, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken for a medical condition then it should be coded under the medications section. All pure homeopathic medications that are given for a medical condition should be coded as MED00227.

  - A homeopathic product can be identified by label. Doses for homeopathic products have the Roman numeral listed in the recommended doses, with a C, M, or X, such as 6X, 12C, 5M, etc.
    - In Europe and some other parts of the world you will see the letter D or DH. This refers to decimal or 1/10 which is the same as X, used in the U.S. Also in Europe the position of the number and letter designation are reversed from the US designation. So you will see such designations as D5 or D10 which are equivalent to 5X and 10X. You will also encounter CH and CK, these are equivalent to C, referring to the Centesimal or 1/100 dilution rate.

- Sites should review the complete ingredient list of the product before classifying it as purely herbal. If the product contains added vitamins, minerals, probiotics, etc then it should be coded in the dietary supplements section. If the product is deemed to be purely herbal, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken for a medical condition then it should be coded under the medications section. A purely herbal product that is given for a medical condition will be assigned a TEDDY medication code based upon its active ingredients. When requesting a medication code for a purely herbal medication, coordinators should provide the DCC with as many of the active ingredients contained in the herbal medication as possible. If none of the active ingredients are able to be identified, then the herbal medication should be coded as "MED00303 - nonspecific herbal medication". If all or a portion of the active ingredients can be identified, the coordinator should send a medication code request to the DCC along with the list of active ingredients.
- Use MED00499 to code Physical alternative remedy: acupuncture, acupressure, energy therapies

(electromagnetic therapy, Qi gong, Reiki, etc), chiropractic adjustment, aromatherapy, therapeutic massage, etc

- An alternative medication/therapy (such as colloidal silver, chelation, etc.) will be assigned a TEDDY medication code based upon its active ingredients. When requesting a code for an alternative medication/therapy, coordinators should provide the DCC with as many of the active ingredients contained in the alternative medication/therapy as possible. If none of the active ingredients are able to be identified, then the alternative medication/therapy should be coded as "MED00525 - nonspecific alternative medication/therapy". If all or a portion of the active ingredients can be identified, the coordinator should send a medication code request to the DCC along with the list of active ingredients.
- Dietary supplements taken for medical conditions/illnesses should not be entered in the medication section of the questionnaire. Instead they should be entered in the dietary supplements section of the questionnaire (this includes products such as Tums and Rolaids whose active ingredients consist only of vitamins, minerals and/or other dietary supplements).

  NOTE: The Diet Committee is not interested in pure homeopathic products. Sites should review the complete ingredient list of the product before classifying it as purely homeopathic. If the product contains added vitamins, minerals probiotics, etc then it should be coded in the dietary supplements section. If the product is deemed to be purely homeopathic, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken for a medical condition then it should be coded under the medications section.

  - A homeopathic product can be identified by label. Doses for homeopathic products have the Roman numeral listed in the recommended doses, with a C, M, or X, such as 6X, 12C, 5M, etc.
    - In Europe and some other parts of the world you will see the letter D or DH. This refers to decimal or 1/10 which is the same as X, used in the U.S. Also in Europe the position of the number and letter designation are reversed from the US designation. So you will see such designations as D5 or D10 which are equivalent to 5X and 10X.

You will also encounter CH and CK, these are equivalent to C, referring to the Centesimal or 1/100 dilution rate.

The Diet Committee is not interested in pure herbal products. Sites should review the complete ingredient list of the product, before classifying it as purely herbal. If the product contains added vitamins, minerals, probiotics, etc then is should be coded in the dietary supplements section. If the product is deemed to be purely herbal, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken for a medical condition then it should be coded under the medications section.

- Exposure to alcohol and cigarette smoke during pregnancy
- Work outside the home during pregnancy
- Special diets during pregnancy
    - If a certain type of food is avoided, the date that the food stopped being eaten by the mother should be recorded in the "Started" column not the date that the symptoms occurred.
- Water source during pregnancy
- Mother's dietary intake during the last month of pregnancy (for USA sites and Swedish sites), or eighth month of pregnancy (for Finnish and German sites)
    - NOTE: If a mother says she is on a gluten-free diet (in question 12c), then the group will assume that any foods she says she ate in question 14a (breads, cereals, pastas and bakery products section) are the gluten-free type. What this means to the clinics is that mothers should be instructed to indicate in question 14a the frequency with which they ate all/any bread, pasta etc, regardless of whether or not these foods are gluten free. Gluten-free products should not be indicated under "other" (unless it is a specific food that does not fit into any category up above). At the analytic stage, if the mother said in question 12c that she was on a gluten free diet, we will likely treat the responses in these categories differently (i.e. no or minimal gluten exposure).
- Use of dietary supplements throughout pregnancy
    - Do not code any supplements that are purely homeopathic preparations in the dietary supplements section. Sites should review the complete ingredient list of the product before classifying it as purely homeopathic. If the product contains added vitamins, minerals probiotics, etc then it should be coded in the dietary supplements section. If the

product is deemed to be purely homeopathic, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken for a medical condition then it should be coded under the medications section. A homeopathic product can be identified by label. Doses for homeopathic products have the Roman numeral listed in the recommended doses, with a C, M, or X, such as 6X, 12C, 5M, etc. In Europe and some other parts of the world you will see the letter D or DH. This refers to decimal or 1/10 which is the same as X, used in the U.S. Also in Europe the position of the number and letter designation are reversed from the US designation. So you will see such designations as D5 or D10 which are equivalent to 5X and 10X. You will also encounter CH and CK, these are equivalent to C, referring to the Centesimal or 1/100 dilution rate.

- Do not code any supplements that are purely herbal products in the dietary supplements section. Sites should review the complete ingredient list of the product, before classifying it as purely herbal. If the product contains added vitamins, minerals, probiotics, etc then it should be coded in the dietary supplements section. If the product is deemed to be purely herbal, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken for a medical condition then it should be coded under the medications section.
- Dietary supplements taken for a medical condition/illness should be entered in the dietary supplements section of the questionnaire, not in the medications section (this includes products such as Tums and Rolaids whose active ingredients consist only of vitamins, minerals and/or other dietary supplements).
- If you have a question about a dietary supplement, or coding a supplement, consult the TEDDY nutritionist at the clinic to help resolve the item. As necessary, the DCC will work with the nutritionists to add codes to cover products as needed.

- Mother's weight and height and weight gain during pregnancy
- Psychological stress experienced during pregnancy
- Maternal perceptions of the baby's risk for T1D
- Maternal anxiety about the baby's risk
- Maternal reactions to the decision to have the baby genetically tested for T1D risk

10.4.2.2 Administration of First Questionnaire - Mother

The First Questionnaire – Mother is designed to be mailed home prior to the baby's first study visit. Prior to mailing, study staff should:

- Include Instruction Sheet and black pen
- Double check the Subject ID "stamped" in the right hand corner of the form, to be sure you are mailing the form to the correct subject

.

If the mother does not bring in the completed questionnaire to the first study visit:

- She may complete the questionnaire at the time of the first visit
- Every effort should be made to get this questionnaire completed by the end of the first visit as parents will be asked to complete several other tasks at home following this first study visit
- If there is insufficient time for the mother to complete the questionnaire at the study visit, she may be given an addressed stamped envelope and asked to complete it at home and return it by mail
- If the mother does not complete the questionnaire and return it within 2 weeks of the clinic visit, the questionnaire may be completed by study staff by telephone interview

10.4.2.3 Review and Coding of First Questionnaire- Mother

At the baby's first study visit, the study staff should review the questionnaire to assure all items are complete, the date the questionnaire was completed is entered correctly, and, if an answer has been changed, the "correct" answer is clear. See Section 10.3 above.

In addition, there are many places where the mother writes in her answer. These include the following items:

2.r. Other infections
7. Other vaccines
8.a. Antibiotics taken
8.b. Anti-inflammatory steroid pills or injections
8.c. Medication for morning sickness
8.d. Medication for diabetes
8.e. Other medications
12.h. Other types of special diets
13. Name of home city/town and zip code
14.a.13. Other cereal products
14.b.12. Other foods prepared with milk or cheese
14.d.11. Other dishes with fish
15. Name of prenatal vitamins, single vitamins, multivitamins, multiminerals or other dietary supplements (such as fish oil, antioxidants or others)

Study staff must carefully review these items to assure they understand what the mother wrote. Staff should ask questions if necessary to be sure they can adequately code the mother's answers.

In particular, clinic staff should anticipate that there will be some dietary items that mothers may question, or additional explanation may be needed to ensure appropriate coding. People tend to have a better memory for medications, vaccines and infections than they do for the specific foods they ate. For example, consider gravies and sauces, snacks, chips, pastries, and pancakes. Sometimes these foods contain milk or wheat products and sometimes they do not. Sometimes it's hard to know the ingredients, unless one carefully reads the product label, and most people don't read labels. Also consider foods eaten outside the home; the mother may not know if the recipe contained cheese or milk, wheat or corn products, or something else.

To resolve these questions, first, ask the mother to provide her best estimate of ingredients and foods. Second, consult with the TEDDY nutritionist at the clinic site to help select the best code.

We can also anticipate that there may be questions about dietary supplements, since there are so many brands and types of products in the marketplace. There is a lengthy list of codes to select from for the different brands, but codes cannot cover every brand. If you have a question about coding for a dietary supplement, consult the TEDDY nutritionist at the clinic to help resolve the item. As necessary, the DCC will work with the nutritionists to add codes to cover products as they enter the marketplace.

10.4.3 First Questionnaire-Father

We are primarily interested in father data from fathers (biological or adoptive) who live with the baby. However, if a biological father does not live with the baby and wishes to participate, we would welcome his response.

10.4.3.1 Content of First Questionnaire-Father

This brief questionnaire is designed to assess the father's:

- Perceptions of the baby's risk for T1D
- Anxiety/worry about the baby's risk
- Reactions to the decision to have the baby genetically tested for T1D risk

10.4.3.2 Administration of the First Questionnaire-Father

The First Questionnaire – Father is designed to be mailed home prior to the baby's first study visit. If the father lives with the child, the questionnaire can be included in the packet mailed with the First

Questionnaire – Mother or First Questionnaire-Primary Caretaker. If the father lives separately, with the mother's consent, the questionnaire may be mailed to the father directly with a return stamped addressed envelope. Prior to mailing, study staff should:

- Include Instruction Sheet and black pen
- Double check the Subject ID "stamped" in the right hand corner of the form, to be sure you are mailing the form to the correct subject

If a completed First Questionnaire – Father is not brought to the first study visit or is not mailed in by the father:

- The father may complete the questionnaire at the time of the first visit if he attends the first visit.
- If the father is not present at the first study visit, and the father lives with the child, the questionnaire may be sent home with an addressed stamped envelope and a request to the father that he complete the questionnaire and return it by mail.
- If the father does not complete the questionnaire and return it, the questionnaire may be completed by study staff by telephone interview.
- Father participation is encouraged but not required for a child to continue in the study protocol.
- The disposition (e.g., refused, mother refused contact with the father, unable to contact the father, no attempt made to contact the father, father never returned the questionnaire) of the First Questionnaire – Father should be indicated on the Participant's Details section of the TEDDY website.

10.4.3.3 Review of First Questionnaire- Father

The study staff should review the questionnaire to assure all items are complete, the date the questionnaire was completed is entered correctly, and, if an answer has been changed, the "correct" answer is clear. See Section 10.3 above. If questions arise and the father does not attend the first study visit, the reviewer may contact the father by telephone to clarify answers.

10.4.4 First Questionnaire – Primary Caretaker

This brief questionnaire is to be used in the relatively rare situation where someone other than the child's mother is the child's primary caretaker. If the child's father is the primary caretaker and the biological mother is not available to fill out the First Questionnaire - Mother, then the father should fill out the Primary Caretaker form and does not need to fill out the First Questionnaire - Father, as all of the Father questionnaire items are contained in the First Questionnaire - Primary Caretaker.

10.4.4.1 Content of First Questionnaire – Primary Caretaker

The First Questionnaire – Primary Caretaker collects information on:

- If the child's birth mother had gestational, type 1 or type 2 diabetes
- The primary caretaker's perceptions of the baby's risk for T1D
- The primary caretaker's anxiety about the baby's risk
- The primary caretaker's reactions to the decision to have the baby genetically tested for T1D risk

10.4.4.2 Administration of First Questionnaire – Primary Caretaker

The First Questionnaire –Primary Caretaker is designed to be mailed home prior to the baby's first study visit. Prior to mailing, study staff should:

- Include Instruction Sheet and black pen
- Double check the Subject ID "stamped" in the right hand corner of the form, to be sure you are mailing the form to the correct subject.

If the primary caretaker does not bring in the completed questionnaire to the first study visit:

- She (he) may complete the questionnaire at the time of the first visit; if this is the case, a new form will need to be generated.
- Every effort should be made to get this questionnaire completed by the end of the first visit as primary caretakers will be asked to complete several other tasks at home following this first study visit.
- If there is insufficient time the primary caretaker to complete the questionnaire at the study visit, she (he) may be given an addressed stamped envelope and asked to complete it at home and return it by mail.
- If the primary caretaker does not complete the questionnaire and return it within 2 weeks of the clinic visit, the questionnaire may be completed by study staff by telephone interview.

10.4.4.3 Review and Coding of First Questionnaire- Primary Caretaker

At the baby's first study visit, the study staff should review the questionnaire to assure all items are complete, the date the questionnaire was completed is entered correctly, and, if an answer has been changed, the "correct" answer is clear. See Section 10.3 above. Study staff should review the questionnaire to assure that the relationship of the primary caretaker to the child is specified and legible so that it can be coded.

10.4.5 Three Month Interview

The Three Month Interview is designed to be interviewer administered at the baby's first study visit. This structured interview is completed with the mother or the child's primary caretaker.

10.4.5.1 Content of the Three Month Interview

The Three Month Interview collects information on:

- The baby's birth
- The baby's health and hospitalizations since birth
- For the option "Failure to thrive (failure to gain weight)" under "Since your baby was born, did he/she have any of the conditions listed below?" If the primary caretaker answers "yes", the interviewer should probe, "Has your pediatrician been concerned about your baby's weight gain?" The "yes" option should only be marked if the primary caretaker indicates that the baby's pediatrician has expressed concern.
    - When coding for a surgical procedure use the ICD-10 code for the reason why the procedure was done. For example if a child had an ear tube placement procedure done the ICD-10 code that applies to the reason why the tubes were replaced should be used, such as "H66.9 - otitis media, unspecified".
    - Circumcision should NOT be coded as a surgery.
    - For the question "Has your child ever been hospitalized (except at deliver)?
        - If the child had a normal delivery, but had to stay past 48 hours (due to an illness/condition of the child, not the mother) then the hospitalization past 48 hours would be recorded here.
        - If the hospitalization stay at delivery included the child being admitted to the NICU then the NICU hospitalization would be recorded here.
- Medications the baby has been given (all types of prescription medications – oral, topical, injection, etc – but only oral non-prescription medication)
    - If the child receives a pure homeopathic preparation and it is being given to alleviate symptoms associated with a condition that can be defined by an ICD-10 code, the name of the homeopathic (if known) along with indication that it is a homeopathic preparation should be written under "name of medication", the reason that it was given, the age of the infant (in weeks) when he/she received the medication, and the number of days the preparation was given should also be recorded. Sites should review the complete ingredient list of the product before classifying it as purely homeopathic. If the product contains added vitamins, minerals probiotics, etc then it should be coded in the dietary supplements section. If the product is deemed to be purely homeopathic, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken for a medical condition then it should be coded under the medications section. All pure homeopathic medications that are given for a medical condition should be coded as MED00227.

- A homeopathic product can be identified by label. Doses for homeopathic products have the Roman numeral listed in the recommended doses, with a C, M, or X, such as 6X, 12C, 5M, etc.
    - In Europe and some other parts of the world you will see the letter D or DH. This refers to decimal or 1/10 which is the same as X, used in the U.S. Also in Europe the position of the number and letter designation are reversed from the US designation. So you will see such designations as D5 or D10 which are equivalent to 5X and 10X. You will also encounter CH and CK, these are equivalent to C, referring to the Centesimal or 1/100 dilution rate.

- Sites should review the complete ingredient list of the product before classifying it as purely herbal. If the product contains added vitamins, minerals, probiotics, etc then it should be coded in the dietary supplements section. If the product is deemed to be purely herbal, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken for a medical condition then it should be coded under the medications section. A purely herbal product that is given for a medical condition will be assigned a TEDDY medication code based upon its active ingredients. When requesting a medication code for a purely herbal medication, coordinators should provide the DCC with as many of the active ingredients contained in the herbal medication as possible. If none of the active ingredients are able to be identified, then the herbal medication should be coded as "MED00303 - nonspecific herbal medication". If all or a portion of the active ingredients can be identified, the coordinator should send a medication code request to the DCC along with the list of active ingredients
- Use MED00499 to code Physical alternative remedy: acupuncture, acupressure, energy therapies (electromagnetic therapy, Qi gong, Reiki, etc), chiropractic adjustment, aromatherapy, therapeutic massage, etc
- An alternative medication/therapy (such as colloidal silver, chelation, etc.) will be assigned a TEDDY medication code based upon its active ingredients. When requesting a code for an alternative medication/therapy, coordinators should provide the DCC with as many of the active ingredients contained in the alternative medication/therapy as possible. If none of the active ingredients are able to be identified, then the alternative medication/therapy should be coded as "MED00525 - nonspecific alternative medication/therapy".

If all or a portion of the active ingredients can be identified, the coordinator should send a medication code request to the DCC along with the list of active ingredients.

- If there is more than one reason for why the medication was given to the child use the next row: fill out all of the information again – codes, ages, etc., enter the 2nd reason why the medication was given to the child and mark "Additional reason for medication above" (if you have a third reason then follow the same process in the next available row, etc).
- Dietary supplements taken for medical conditions/illnesses should not be entered in the medication section of the questionnaire. Instead they should be entered in the dietary supplements section of the questionnaire (this includes products such as Tums and Rolaids whose active ingredients consist only of vitamins, minerals and/or other dietary supplements).

  NOTE: The Diet Committee is not interested in pure homeopathic products. Sites should review the complete ingredient list of the product before classifying it as purely homeopathic. If the product contains added vitamins, minerals probiotics, etc then it should be coded in the dietary supplements section. If the product is deemed to be purely homeopathic, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken for a medical condition then it should be coded under the medications section.

  - A homeopathic product can be identified by label. Doses for homeopathic products have the Roman numeral listed in the recommended doses, with a C, M, or X, such as 6X, 12C, 5M, etc.
    - In Europe and some other parts of the world you will see the letter D or DH. This refers to decimal or 1/10 which is the same as X, used in the U.S. Also in Europe the position of the number and letter designation are reversed from the US designation. So you will see such designations as D5 or D10 which are equivalent to 5X and 10X. You will also encounter CH and CK, these are equivalent to C, referring to the Centesimal or 1/100 dilution rate.

  The Diet Committee is not interested in pure herbal products. Sites should review the complete ingredient list of the product, before classifying it as purely herbal. If the product contains added vitamins, minerals, probiotics, etc then it should be coded in the dietary supplements section.

If the product is deemed to be purely herbal, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken for a medical condition then it should be coded under the medications section.

- If a medication that has been indicated as being given "as needed" is stopped, the site does not need to have the family attempt to estimate the number of days that the medicine was given. The answer to the number of days the medication was given should remain as "as needed".
- If parent indicates that a medication was given for a specific number of days and then was given on an "as needed" basis – the medication information along with the number of days that the medication was given should be recorded on one row of the form and the medication information along with the "as needed" indication should be recorded on a separate row of the form.
- If parent indicates that the same medication was given several times on an as needed basis, the site should only indicate this once on the form to cover the entire period of multiple "as needed" administrations.
- If the medication was marked as "still taking", an inquiry should be made at future TEDDY visits to determine if the child is still given the medication. If the child has stopped taking the medication, remember to record the number of days the child was given the medication along with the other medication information (medication code, reason for taking medication code and age of child when medication was started) on the new TEDDY Book extraction form.
- When a parent indicates that an unknown medication was given to the child the site should probe the parent to try to obtain the class or type of medication that was given, for example "unknown antibiotic", "unknown steroid", etc (since the reason the medication was given will be indicated with the ICD-10 code(s)). If the parent does not know this type of information and all the parent knows is that some type of medication was given for X illness/condition, then the site can use the corresponding code for "unknown medication for X illness/condition".
- When coding for a medication given for a surgical procedure use the ICD-10 code for the reason why the procedure was done. For example if a child received propofol for the sedation during an ear tube placement procedure, the ICD-10 code that applies to the reason why the tubes were replaced should be used to indicate the reason why the medication was given, such as "H66.9 - otitis media, unspecified".

- The type of food the baby has been given, including duration of breast feeding and types and duration of infant formulas given
    - If the baby is fed infant formula it is important to obtain the precise brand and type of the formula or product. This is because of major differences exist in baby formula ingredients, even among the same brand. Many formulas and are now fortified with nutrients such as DHA, an omega-3 fat that is of particular interest to TEDDY. For example, in the USA, list the brand "Enfamil Lipil with Iron," or "Enfamil Lacto Free Lipil with Iron," not just "Enfamil." The "Lipil" in the name indicates the product is fortified with DHA, the important omega-3 fat.

      If there are questions, or if there is a formula that is "missing" from the code list, consult the nutritionist at the clinic site. For more information about the dietary interview, see Chapter 12 of the TEDDY Manual of Operations.
    - If the formula is changed, note that the change could be in brand or in the type (ready to feed, powder, or liquid concentrate) of the formula, the reason for changing formula code should be entered in the row that the new formula information is recorded in; it should not be entered in the row with the old formula information.
- Type of water the baby has been given
- Single vitamins, multivitamins, multiminerals or other dietary supplements (such as fish oil, antioxidants or others)
    - Do not code any supplements that are pure homeopathic preparations under the dietary supplements section. Sites should review the complete ingredient list of the product before classifying it as purely homeopathic. If the product contains added vitamins, minerals probiotics, etc then it should be coded in the dietary supplements section. If the product is deemed to be purely homeopathic, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken for a medical condition then it should be coded under the medications section.
    - A homeopathic product can be identified by label. Doses for homeopathic products have the Roman numeral listed in the recommended doses, with a C, M, or X, such as 6X, 12C, 5M, etc. In Europe and some other parts of the world you will see the letter D or DH. This refers to decimal or 1/10 which is the same as X, used in the U.S. Also in Europe the position of the number and letter designation are reversed from the US designation. So you will see such designations as D5 or D10 which are equivalent to 5X and 10X. You will also encounter

CH and CK, these are equivalent to C, referring to the Centesimal or 1/100 dilution rate.

- Do not code any supplements that are pure herbal products under the dietary supplements section. Sites should review the complete ingredient list of the product,before classifying it as purely herbal. If the product contains added vitamins, minerals, probiotics, etc then it should be coded in the dietary supplements section. If the product is deemed to be purely herbal, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken for a medical condition then it should be coded under the medications section.
- Dietary supplements taken for a medical condition/illness should be entered in the dietary supplements section of the questionnaire, not in the medications section (this includes products such as Tums and Rolaids whose active ingredients consist only of vitamins, minerals and/or other dietary supplements).
- There may also be questions about infant dietary supplements during the interview, since there are many brands and types of products available. There is a list of codes to select from for the different brands, but codes cannot cover every brand. It is best to ask the mother to bring in the product and/or label so you can identify the product positively, but that may not always be possible.
- If you have a question about a dietary supplement, or coding a supplement, consult the TEDDY nutritionist at the clinic to help resolve the item. As necessary, the DCC will work with the nutritionists to add codes to cover products as needed.

- Any foods introduced and the baby's age at introduction
- Any special diet given the baby, including cow's milk and cereal/wheat avoidance
  - If a certain type of food is avoided, the date that the food stopped being given to the child should be recorded in the "Started" column not the date that the symptoms occurred.
- Major life experiences that happened to the baby's mother during her pregnancy or since the baby's birth
- Major life experiences experienced by the baby

Tips on recording Life Experiences

- Since the life experiences for the parent and child are divided into two separate questions in the 3 Month Interview, parent life event numbers (1-22) should be entered for question 17 only (parent life experience question) and child life event numbers (23-33) should be entered for question 18 only (child life experience question). Please refer to the TEDDY

Code book if you have questions regarding what is a parent event and what is a child event.

- If a life event affects both a parent and a child, it is important to record it only once i.e. either as a mother (parent) life experience or as a child life experience. For example if the family has moved – #16 - (the child included) the event can preferably be reported as a parent life experience. Another example: if the child has been hospitalized report #24 as a child life experience and not #4 "a family member was hospitalized".
- If there is a question about whether an event should be listed as a parent or child life experience, the decision should be based on who the event affects the most.
- For the Parent Life Experiences question if a life event was ongoing during the pregnancy and/or continued after the birth of the child fill in all the trimesters the event occurred during and mark that it occurred since the birth of the child day 1 (this question in the 3 month Interview asks for the age of the child in weeks, so day 1 would be indicated as 0 weeks – refer to conversion table in section 10.3.7.) For example if the parent experienced financial difficulties in the 2nd and 3rd trimester and they continued after the birth of the child, you would mark 2nd trimester, 3rd trimester and since the birth of the child day 1 (0 weeks).
- If the event occurred since the birth of the child make sure that you record the age of the child when the event first occurred (even for continuous events),
- Life events can be acute or "continuous." Acute life events are things that occur once within a relatively short time frame. Continuous life events are those that reoccur over a substantial amount of time, defined as ≥ 1 month. For example, "serious arguments/conflict with spouse/significant other" could be an acute stress occurring on one occasion during the interview period. Or it could be a continuous stress if it occurred repeatedly over ≥1 month interval. On the three month interview, check "continuous" if the life event is an ongoing stress at the time of the interview or lasted ≥ 1 month during pregnancy or since the birth of the child. Be sure to indicate the age of the child at the time the stress first occurred if it occurred since the birth of the child. For all subsequent visits, "continuous" should be checked whenever a life event is ongoing at the time of the interview or lasted ≥ 1 month during the time since the last study visit.
- Always be sure to mark the impact on both the child and the parent (even if the mother is pregnant when the event occurred, impact on child should be indicated). If there was

no impact on the child or parent, "none" should be entered as the impact.

- If you do not have a record of the impact information, you should obtain it by asking at the child's next visit or, if you prefer, by calling the parent.

10.4.5.2 Administration of the Three Month Interview

As part of the baby's first study visit, the interviewer will conduct this structured interview with the primary caretaker (usually the child's biological mother), documenting all answers on the interview form provided.

- Explanations and questions are to be read to the primary caretaker directly from the Three Month Interview form.
- No items should be skipped.
- If a participant refuses a question, the interviewer should so note on the interview form, initial and date.
- Since many items must be coded by the interviewer, the interviewer should be familiar with the codes for the Three Month Interview (see below) so sufficient information can be obtained from the primary caretaker to accurately code all answers.
- A release of information should be readily available in case the primary caretaker reports the child has been hospitalized, to permit access to the child's medical record.
- To conduct the interview, the interviewer will need the Experiences of the Parent Card and the Experiences of the Child Card. These are shown to the primary caretaker when asking question 17 (Parent Card) and question 18 (Child Card).
- It is important to establish rapport with the primary caretaker and assure her (or him) that there are "no right or wrong answers" to questions. At no time should the interviewer imply that something the primary caretaker reports doing (or not doing) is incorrect. If the primary caretaker queries the interviewer as to recommended practice, the interviewer should reiterate that there are no right or wrong answers and the primary caretaker should continue to care for her (or his) baby in her (or his) usual manner and they can discuss these questions with their healthcare provider.
- In the US, care should be taken to enter all dates correctly in the European format: day, month/year.
- Age is sometimes recorded in days, weeks, or months. Often options are provided (e.g., days or weeks, weeks or months) and the interviewer selects the timeframe used by the primary caretaker. However, for introduction foods, age is always entered in half months. Use normal rounding methods. For example, a child who was given apple sauce at age 2 months 2 weeks would be coded as age 2.5 months. A child who was given apple sauce at 2 months 3 weeks would be coded as 3.0 months.

10.4.5.3 Coding the Three Month Interview

The following questions responses will require coding on this interview:

6.bb.	Other condition experienced by baby since birth
8. a-d.	Medication codes and reasons for medication codes
11.a-d.	Formula brand codes and reasons for changing formula
12, 13.	Other kinds of water or water sources codes for drinking water and food preparation water.
14.	Single vitamins, multivitamins, multiminerals or other dietary supplements (such as fish oil, antioxidants or others)
15.33	Other food introduced
16.f.	Other special diet not listed
17.	Other life event of parents not listed on card
18.	Other life event of child not listed on card

Coding should generally be done after the interview is completed so as to not interrupt the flow or take time for the participant. Consequently, the interviewer should write all responses legibly and be familiar with the coding system so that participants' answers can be clarified if necessary to assure accurate coding of responses.

10.4.6 Six Month Questionnaire for Mother, Father, or Primary Caretaker

The Six Month Questionnaire is designed to be used by multiple respondents: mother, father, and/or primary caretaker. For example, for children with two parents involved in their lives, two six month questionnaires may be completed for each child – one by the mother and one by the father.

10.4.6.1 Content areas of the Six Month Questionnaire

The Six Month Questionnaire provides information on:

- Respondent perception of the child's risk for TID
- Respondent worry or anxiety about the baby's risk for TID
- Evidence of postpartum depression
- Respondent beliefs about whether anything can be done to prevent TID in the child
- Anything done to try and prevent T1D in the child
- Anything done to monitor the child's risk of developing T1D
- Respondent reactions to study participation

Actions Done to Prevent Child from Developing T1D (question number 9) versus Things Done to Monitor Child's Risk of Developing T1D (question number 10)

Actions Done to Prevent Child from Developing T1D refers to behaviors designed to actually prevent the disease. Monitoring refers to early detection of the disease while prevention refers to activities designed to stop the disease from occurring. Examples might include changing the child's diet, avoiding sweets, breastfeeding, trying to protect the child from infections. It is possible that some parents view participating in TEDDY as a prevention activity because their child may be eligible for a prevention trial should the environmental trigger(s) for TID be identified. However, TEDDY itself is not a prevention trial.

Occasionally a parent may indicate a monitoring behavior as a prevention behavior. When this happens try to have a clarifying conversation with the parent in order to code this properly under the "Things Done to Monitor Child's Risk of Developing T1D" question. If it is not possible to have this conversation this can be coded under the "Actions Done to Prevent Child from Developing T1D" question; the specific code request should be sent to the DCC who will then discuss it with the Psychosocial Committee.

Things Done to Monitor Child's Risk of Developing T1D refers to efforts to detect diabetes in the at-risk child. Common activities might include watching the child for symptoms of diabetes – frequent urination, drinking a lot, fatigue. Sometimes parents will test the child's blood or urine for evidence of glucose. Other times they might take the child to the doctor more often. For many parents, participating in TEDDY may be viewed as a way to monitor the child for diabetes. Because the child is being tested frequently, the parent might expect the child's diabetes to be detected early.

When parents describe a behavior as a monitoring or prevention behavior, be sure to ask questions for clarification. For example, if a mother says she is making sure her child "eats healthy" to prevent diabetes, ask her what she means by that. Her response will make it easier to code her behavior into the correct category. For example, she might say that she limits her child's sugar or she might say she is feeding her child only organic foods or that she is avoiding additives or that she is making sure her child eats lots of vegetables. All of these responses are examples of what someone might mean by "eating healthy." However, if you don't get further clarification, you haven't really captured what kinds of behaviors she is engaging in.

If someone says participating in the TEDDY study is how they are monitoring or preventing the child's diabetes, be sure to ask for

clarification. Parents may view TEDDY participation in many different ways and we need to understand each parent's perspective in order to code the response accurately.

Occasionally a parent may indicate a prevention behavior as a monitoring behavior. When this happens try to have a clarifying conversation with the parent in order to code this properly under the "Actions Done to Prevent Child from Developing T1D" question. If it is not possible to have this conversation this can be coded under the "Things Done to Monitor Child's Risk of Developing T1D" question; the specific code request should be sent to the DCC who will then discuss it with the Psychosocial Committee.

10.4.6.2 Administration of the Six Month Questionnaire

The Six Month Questionnaire is completed by the mother or primary caretaker at the baby's second or six month study visit. The father's Six Month Questionnaire can be completed at the six month study visit, if the father attends the visit, or may be sent home for the father to complete. The Clinical Center also has the option of sending the Six Month Questionnaire(s) home to the mother or primary caretaker and Father (if applicable), to be completed prior to the six month visit and to be brought in with them to their scheduled appointment. All respondents should be provided with the Instruction Sheet and a black pen.

- If the Six Month Study Questionnaire is not completed at the six month study visit by the mother or primary caretaker, it may be mailed home for completion, with appropriate instructions and an addressed stamped return envelope.
- If the questionnaire is not completed and returned, the questionnaire may be completed by study staff by telephone interview.
- If the child lives with the father and the father does not come to the study visit, the mother or primary caretaker should be provided with the Six Month Questionnaire to give to the father with an addressed stamped return envelope to mail his responses
- If the child does not live with the father but the father is actively involved in the child's life, the Six Month Questionnaire may be sent home to the father with a stamped addressed return envelope
- If the father does not complete the questionnaire and return it, the questionnaire may be completed by study staff by telephone interview.
- Father participation is encouraged but not required for a child to continue in the study protocol.
- Disposition of the father's Six Month Study Questionnaire (e.g., refused, mother refused contact with the father, unable to contact

the father, no attempt made to contact the father, father never returned the questionnaire) should be indicated in the Participant's Details section of the TEDDY website.

- In some cases, a new father may enter the child's life. For example, the child's biological father may fill out the First Questionnaire - Father. The child's mother may marry someone else who may wish to participate as well. This step-father should indicate his relationship to the child is "other" and then specify step-father. He should indicate his relationship to the child as "other" and then specify step-father on all subsequent questionnaires he completes. This will permit us to distinguish questionnaire responses from more than one father.

10.4.6.3 Review of the Six Month Questionnaire

The study staff should review all respondents' Six Month questionnaires to assure all items are complete, the date the questionnaire was completed is entered correctly, and, if an answer has been changed, the "correct" answer is clear. See Section 10.3 above.

10.4.6.3.1 Responding to Post-Partum Depression

Items 7.a through 7.j assess postpartum depression using the Edinburgh Postnatal Depression Scale. Each item is scored from 0 to 3. Some items are reverse-scored. Item 7.j is a critical item. If the respondent answers anything other than NEVER to item 7.j, action should be taken. If the respondent answers NEVER to item 7.j., study staff should score all 10 items. For ease of scoring, a scoring key is provided in the code box next to each item. Study staff can score each item in the box and sum all items. If a respondent receives a total score ≥ 13, action should be taken. All referrals should be noted on the Physical Exam form and on the online Adverse Event Reporting Form (see MOO section 9.7 for instructions).

SCORING DIRECTIONS – EDINBURGH POSTNATAL DEPRESSION SCALE

Some parents get the baby blues after the birth of the child. Here are some questions about the baby blues. Please, <u>think about the time since this child was born</u> for each question and then mark an answer.

a. You have been able to laugh and see the funny side of things

[0] As much as I always could
[1] Not quite so much now
[2] Definitely not so much now
[3] Not at all

b. You have looked forward with enjoyment to things.

[0] As much as I always did
[1] Rather less than I used to
[2] Definitely less than I used to
[3] Hardly at all

c. You have blamed yourself unnecessarily when things went wrong.

[3] Most of the time [2] Some of the time [1] Not very often [0] Never

d. You have been anxious and worried for no good reason.

[0] Not at all [1] Hardly ever [2] Sometimes [3] Very often

e. You have felt scared or panicky for no very good reason.

[3] Quite a lot [2] Sometimes [1] Not much
[0] Not at all

f. Things have been getting on top of you.

[3] Most of the time you haven't been able to cope at all
[2] Sometimes you haven't been coping as well as usual
[1] Most of the time you have coped quite well
[0] You have been coping as well as ever

g. You have been so unhappy that you have had difficulty sleeping.

[3] Most of the time [2] Sometimes [1] Not very often [0] Never

h. You have felt sad and miserable.

[3] Most of the time [2] Some of the time [1] Not very often [0] Never

i. You have been so unhappy that you have been crying.

[3] Most of the time [2] Quite often [1] Only occasionally [0] Never

*** j. The thought of harming yourself has occurred to you.**

[3] Quite often* [2] Sometimes* [1] Hardly ever*
[0] Never

**CRITICAL ITEM – If the respondent answers anything other than NEVER, take action*

Each site has developed a specific strategy for managing this situation (see Appendix A). A sample approach taken from the

External Advisory Board's approved study Protocol is provided below:

If the respondent answers anything other than NEVER to item 10, or has a total score ≥13, ask:

Have you told your doctor or anyone else about your feeling blue or having thoughts of hurting or harming yourself? (YES or NO).

Are you currently receiving treatment for these feelings? (YES or NO).

IF NO: Would you like information about doctors in your area that you may be able to see about these feelings? (YES or NO).

IF YES: Provide mother with names of providers in her county or related area. You may initially provide her with the crisis hotline number for her county, obtain insurance information, and call her back with the names of providers.

IF NO: We feel it may be highly beneficial for you to speak with someone regarding this matter. It would be advisable to see your general physician or go to the local health department. It may be a good idea for us to contact the crisis center in your area and have them call you to further speak with you about your feelings. Would this be OK with you? Should you continue to feel blue or think about harming yourself, please contact either your primary care physician, therapist, or call us at (xxx) xxx-xxx if you would like the names of specific doctors in your area. Ask for_____.

10.4.6.4 Coding of the Six Month Questionnaire

The respondent may write in responses to the following questions:

Q2: Relationship to child is other, specify

Q9. Kinds of things that done to try and stop or prevent diabetes in child

Q10. Anything done to monitor child's risk of developing diabetes

Study staff should assure any responses are legible. Study staff should be familiar with coding methods for these questions, especially responses to 9 and 10 and ask any questions necessary to assure accurate coding of responses.

10.4.7 Family History Questionnaire

This questionnaire is intended to be given to parents at the 6 month clinic visit and brought back with them at the 9-month visit. Although self-administered, it requires a thorough explanation about the content and lay-out, and then subsequent review when it is returned. Detailed family history data benefits from subjects being able to access family records for dates and information being requested and is therefore designed as a take home questionnaire.

10.4.7.1 Content Areas of the Family History Questionnaire

This questionnaire requests an auto-immune disease and diabetes family history for the following biologically related relatives to the TEDDY child:

- Parents
- Grandparents (maternal and paternal)
- Aunts and uncles (identified as mother or father's siblings)
- Siblings of the TEDDY child (full or half)

As a referent point, the first name only of each relation is written in the first column and for each person listed the following information is requested.

- Birth year
- Gender for aunts, uncles, and siblings
- Age or year of death, if person is deceased
- Any autoimmune diseases this person has/had (with a review list provided)
- Does/did this relation have diabetes (any type)
  - What type if known
  - Age or year of diagnosis
  - Ever taken insulin shots

NOTE: For the question "Does or did this person have diabetes?" in the mother's row applies to if the mother has ever had gestational diabetes, not just gestational diabetes with the TEDDY subject.

- If the mother had gestational diabetes with several pregnancies, the age or year of diagnosis should relate to the first time she developed gestational diabetes

10.4.7.2 Administration and Review of the Family History Questionnaire

During the 6 month clinic visit, study staff will review the family history questionnaire with the parent. If the primary caretaker at the 6 month visit is someone other than a biologically related parent it is important to determine who is available that can best provide this information about the child's biologic relations. If possible, this

person should be contacted and mailed the form with a return envelope included.

The study staff provides an explanation of the family history questionnaire that covers the following points:

- Include an instruction sheet and black ink pen with the questionnaire and quickly review the best way to fill it out.
- Interested in those family members who are biologically related to the child, reviewing the different relations requested and showing the parent the column and row headings
- Interested in autoimmune diseases and diabetes family history, not other diseases and show list of autoimmune diseases pointing out what is included and review the different questions asked of each relation
- Explain that we are sending it home with them because sometimes the information about age or type of disease is more easily available with records or communications with these family members
- Explain that if they don't know the exact age or year requested that it is okay to estimate
- That we will remind them to bring this with them to the 9-month visit.
- Ask them if they have any questions right now and tell them that if they do have questions the number to call the study staff is on the front page
- For questions pertaining to the TEDDY child's aunts and uncles it is not necessary to indicate that the aunt or uncle is a full or half sibling of the TEDDY child's mother or father.

Clinic staff can determine the best time during the clinic visit to incorporate this explanation.

Review of the Family History Questionnaire will ideally occur when the parent brings it to the 9-month visit. A reminder will be sent before this visit to bring this questionnaire with them. If the questionnaire is not brought in or the 9 month visit is missed, then study staff should inquire if the parent would like to send in the completed questionnaire or have them give it to the study staff person over the phone.

Regardless of when the review occurs, it should include making sure that all numbers and written portions are legible and that appropriate questions were completed. For example if a relation is marked as having diabetes (yes) then the three columns asking for information about diabetes in this person should be filled in. Space is provided for two autoimmune diseases per relation to be listed and coded. It

will be rare, but possible that a relation may have more than two autoimmune diseases. In such a case the 2 autoimmune diseases of longest duration should be listed (other than type 1 diabetes).

The study staff person completing the review should fill in the back "office use only" box at this time.

10.4.7.3 Coding the Family History Questionnaire

The only field requiring coding is for any autoimmune diseases listed for each relation. The TEDDY Study Codebook list provides the ICD-10 codes for the diseases listed in the questionnaire.

10.4.8 Update form for Family History Questionnaire (data originally collected in the 9 month Family History Questionnaire)

The Update form for Family History Questionnaire is intended to be given to parents at the clinic visit immediately prior to the 33 month visit, 54 month visit, 8 year 6 month visit, 12 year 6 month visit and 14 year 6 month visit (and it is intended that the completed form be brought back to the clinic at these listed visits). Although self-administered, it requires a thorough explanation about the content and lay-out, and then subsequent review when it is returned. Detailed family history data benefits from subjects being able to access family records for dates and information being requested and is therefore designed as a take home questionnaire. The purpose of this form is to capture data that has changed since the 9 month Family History Questionnaire was completed, so this form asks the same questions as the 9 month Family History Questionnaire.

10.4.8.1 Content Areas of the Update form for Family History Questionnaire

Same as the 9 month Family History Questionnaire - see section 10.4.7.1 for details

10.4.8.2 Administration and Review of the Update form for Family History Questionnaire

During the clinic visit immediately prior to the visit that the Update form for Family History Questionnaire is due, study staff will review the Update form for Family History Questionnaire with the parent if necessary. If the primary caretaker at the visit is someone other than a biologically related parent it is important to determine who is available that can best provide this information about the child's biologic relations. If possible, this person should be contacted and mailed the form with a return envelope included.

The study staff provides an explanation of the family history questionnaire that covers the following points:

- Include an instruction sheet and black ink pen with the questionnaire and quickly review the best way to fill it out*
- Interested in those family members who are biologically related to the child, reviewing the different relations requested and showing the parent the column and row headings
- Interested in autoimmune diseases and diabetes family history, not other diseases and show list of autoimmune diseases pointing out what is included and review the different questions asked of each relation
- Explain that we are sending it home with them because sometimes the information about age or type of disease is more easily available with records or communications with these family members
- Explain that if they don't know the exact age or year requested that it is okay to estimate
- That we will remind them to bring this with them to the next visit.
- Ask them if they have any questions right now and tell them that if they do have questions the number to call the study staff is on the front page
- For questions pertaining to the TEDDY child's aunts and uncles it is not necessary to indicate that the aunt or uncle is a full or half sibling of the TEDDY child's mother or father.

Clinic staff can determine the best time during the clinic visit to incorporate this explanation.

*Sites have two different options for completion of this form. Each site will determine the best option for them:

Option #1 – using both prepopulated online form print-out and blank Teleform print-out:

- Site will login to TEDDY website and open online form of Update form for Family History Questionnaire that is currently due.
- The form is pre-populated with the data from the last submitted form.
- Site will print prepopulated online form.
- Site will print blank teleform.
- Site will give both the prepopulated online form print-out and the blank Teleform print-out to the family.
- Family should review each row of the prepopulated online form print-out.

  - If there is no change to the data in the row then the family should mark "No Change" on the corresponding row on the blank Teleform
    - NOTE: site does not need to transfer any of the prepopulated information from the online form to the Teleform
  - If there is a change to the data in the row then the family should mark "Change to Information" on the corresponding row on the blank Teleform AND write-in the new information on the blank Teleform
    - NOTE: site does not need to transfer any of the prepopulated information from the online form to the Teleform
- Site will keep both the printed online form and written on Teleform together and consider both to be the source documents.
- Site will open prepopulated online form and enter answers received from family into online form ("No Change", "Change to Information" and if "Change to Information" marked, newly provided data).

Option #2 – using only prepopulated online form print-out:

- Site will login to TEDDY website and open online form of Update form for Family History Questionnaire that is currently due.
- The form is pre-populated with the data from the last submitted form.
- Site will print prepopulated online form.
- Site will give the prepopulated online form print-out to the family.
- Family should review each row of the prepopulated online form print-out.
  - If there is no change to the data in the row then the family should mark "No Change" on the corresponding row on the prepopulated online form print-out.
  - If there is a change to any of the data in the row then the family should mark "Change to Information" on the corresponding row on the prepopulated online form print-out AND write-in the new information on the prepopulated online form print-out AND cross-out any old data that has now changed.
- Site will keep written on printed online form as source document.
- Site will open prepopulated online form and enter answers received from family into online form ("No Change", "Change

to Information" and if "Change to Information" marked, newly provided data).

Review of the Update form for Family History Questionnaire will ideally occur when the parent brings it to the next visit. A reminder will be sent before this visit to bring this questionnaire with them. If the questionnaire is not brought in or the next visit is missed, then study staff should inquire if the parent would like to send in the completed questionnaire or have them give it to the study staff person over the phone.

Regardless of when the review occurs, it should include making sure that all numbers and written portions are legible and that appropriate questions were completed.

The study staff person completing the review should fill in the back "office use only" box at this time.

The DCC has programmed the online Update form for Family History Questionnaire so that the previous visit's submitted data prepopulates on the currently due update form. If a site is unable to administer an Update form, when the not done reason is entered in the tracking system for that form, the next due Update form after that will then be prepopulated with the last submitted form's data. The data is prepopulated so that the staff member can see the previously submitted data and indicate whether the data has changed or not since the last form was completed. The site should print-out the prepopulated online form and give it to the parent with the clean copy of the Update form for Family History Questionnaire Teleform; the parent should indicate his/her answers on the Teleform version of the form.

NOTE: Due to the prepopulation functionality of this form, sites will NOT be able to upload the data for the Update form as a Teleform. All Update form data must be submitted to the DCC through online data entry.

The only exception to which Update form is prepopulated with the previous form's data is when the Update form is first made available through the TEDDY website by the DCC in June 2012 – at this time the 9 month Family History Questionnaire data will populate on all of the subject's Update forms for Family History Questionnaire. Once the site has administered the Update form to the parent at the next due visit, entered the data from the Update form in the corresponding online form for which the date the questionnaire was

reviewed falls into the window, then the prepopulation of the later forms will act as described above.

The staff member should complete the date the questionnaire was reviewed, visit location code, TEDDY staff code and visit number at the top of the Update form. Each row on the Update form for Family History Questionnaire has the following answer choices: "No Change", "Change to Information" and "Unknown if Information has Changed or Not". The "No Change" answer choice should be selected when all of the prepopulated data for that particular row is still exactly the same as the last time the form was completed. If the "No Change" answer choice is selected the prepopulated data will be saved to the database as the answer for this Update form. A check box has been added to the online form for "No change to every question on this form" and when selected all "No change" options on the form will be selected. The "Change to Information" answer choice should be selected when some or all of the prepopulated data for that particular row is not the same as the last time the form was completed. If the "Change to Information" answer choice is selected the prepopulated data will NOT be removed and the staff member is expected to change data that has changed since the last completion of the form or enter new data since the last completion of the form. The "Unknown if Information has Changed or Not" should be selected in situations for which it is unknown if the information has changed or not such as in divorced families who no longer have any contact with the ex-spouse or family.

If an error was made on a previously submitted form, do not correct the error on the current form; the error needs to be corrected on the original form that it was submitted in – please see instructions below for corrections. Please note that in order to save the form it is required that either "No Change" or "Change to Information" be selected for every row.

In the child's sibling section a column has been added for "If a sibling DNA sample was collected from this sibling indicate the sibling's Relative ID here" – if this applies to this sibling enter the corresponding relative ID in the data field. Once a relative ID has been submitted for a sibling, the data field will be locked so that the site cannot edit it. Should a correction need to be made to the relative ID entered on the form the site should contact the DCC.

The Autoimmune Disease question could have more than one answer and the answer submitted on a previous Update form could still be applicable in addition to the answer(s) to be entered on the current Update form. For example, on a previous Update form the site

indicated the ICD-10 code for Graves Disease for the child's biological mother, now in addition to Graves Disease the mother has also been diagnosed with Psoriasis. For these situations the site must choose the "Change to Information" answer choice and then indicate both the previous answer and the new answer. So for the example given, the site would mark "Change to Information" and then indicate the ICD-10 code for Graves Disease and the ICD-10 code for Psoriasis in the "Child's Biological Mother" row.

If the site needs to make a correction to a submitted form, if the data for the next Update form has not been submitted to the DCC yet, then the site can go in to the form that they need to make the change on and update the data. For example, if the site has submitted the 33 month Update form to the DCC, but has not yet submitted the 54 month Update form to the DCC and needs to make a correction on the 33 month Update form, the site can go into the 33 month Update form and make the change. If the site needs to make a correction to a submitted form, but the data for the next Update form has already been submitted to the DCC, then the site should NOT make the correction to the form and should contact the DCC. For example, if the site has submitted a 54 month Update form and a 8 year 6 month Update form, but needs to make a correction to the 54 month Update form, the site should not change any data on the 54 month Update form and should instead contact the DCC.

If a 9 month Family History Questionnaire was never completed for the subject, the site should complete the Update form at the next visit. If the 9 month Family History Questionnaire was not collected for a subject, then there will of course be no data prepopulated in the Update form. For every row that the site is able to obtain data for on the Update form the site should indicate "Change to Information" and enter the new data. For every row that the site is unable to obtain data for on the Update form the site should indicate "No Change".

If on the 9 month Family History Questionnaire or an Update form an answer was not able to be obtained to a question, on the next due Update form there will of course be no data prepopulated in the Update form for that question. If there is a question in a row that the site was previously unable to obtain data for, but has now obtained data on the new Update form the site should indicate "Change to Information" in that row and enter the new data. If the site is still not able to obtain any information for any of the questions in the row in the new Update form the site should indicate "No Change" in that row. If there is no information to be obtained for any of the questions in a row because the row is not applicable to a subject (for

example, the 7th-9th "Child's aunt(s) & uncle(s)" rows) the site should enter "No Change" in each row on the Update form.

If a family member develops another diabetes type later on – for example the mother indicated "gestational diabetes" and then at a later visit informed the TEDDY staff that she has developed "type 2 diabetes" – the staff member should click on "Change to Information" in that family member's row and then click the radio button of the new diabetes type. Both the original diabetes information as well as the new diabetes information will be saved in the database.

10.4.8.3 Coding of the Update form for Family History Questionnaire

Same as the 9 month Family History Questionnaire - see section 10.4.7.3 for details

10.4.9 Nine Month Interview

The Nine Month Interview is designed to be interviewer administered at the baby's nine month clinic visit. This structured interview is completed with the primary caretaker (mother, father or other). Sites have the ability to enter a second nine month interview for situations in which the parents are separated/divorced and the TEDDY child lives with one parent part of the time and the other parent the other part of the time.

10.4.9.1 Content Areas of the Nine Month Interview

The Nine Month Interview provides information on:

- The child's living arrangements, marital status of parents, frequency of seeing parent if parents are living separately
- Demographic information on the primary male and female caretakers including first language spoken, country of birth, first child status, years of schooling, work outside of home.
- Household size and age composition (number of children under age 18 and number of adults living in household)
- Type of community (rural/urban)
- Child's exposure to smoke in female and male caretakers and others
- Presence of pets and type of pets in house
- Exposure to farm animals and types of animals

10.4.9.2 Administration and Review of the Nine Month Interview

The interviewer will conduct this structured interview with the mother or primary caretaker at the baby's third or nine month study visit documenting all answers on the interview form provided.

If the Nine Month Interview is not completed at the nine month study visit by the mother or primary caretaker, the interview may be completed by study staff by telephone interview.

- Explanations and questions are to be read to the primary caretaker directly from the Nine Month Interview form.
- No items should be skipped.
- If a participant refuses a question, the interviewer should so note on the interview form, initial and date.
- Since many items must be coded by the interviewer, the interviewer should be familiar with the codes for the Nine Month Interview (see below) so sufficient information can be obtained from the primary caretaker to accurately code all answers.
- In the US, care should be taken to enter all dates correctly in the European format: day, month/year.
- For questions "How many children (under the age of 18 years) live in your household?" and "How many adults (18 and older) currently live in your household?" – if a person (such as a half-sibling or step-sibling) spends approximately half of his/her time in the household he/she should be counted.
- For question "If the TEDDY child's parents are living apart, think about the parent the child sees less often. How often does this parent see the child?" – if parent answers they both see the child equal amounts of time enter 15 days per month. If you are able to complete a form for each parent then mark 15 days per month on each parent's form.
- For questions 9E: Do you (MOM) work outside of the home? and 10E: Do you (DAD) work outside of the home? – the purpose of these questions is to determine the amount of time that the parent is separated from the child (Note: these two questions were removed from the form in April 2018):
    - If the parent works inside of the home and does NOT have another caregiver provide for the child, the response is NO and number of hours is left blank.
    - If parent works inside of the home and has another caregiver provide care for the child, the interviewer should prompt for the number of hours that the parent is separated from the child. The response would be YES, and the number of hours the other caregiver is caring for the child will be documented.
    - If a parent is in the military and is actively deployed, the interviewer should enter 168 (24 hours x 7 days a week) for the number of hours the parent works outside of the home.
    - If a parent spends entire 24 hour days away from the home each week due to work, the amount of time away from the

child should be indicated in the number of hours the parent works outside of the home field. For example, if the parent spends Monday – Friday away from the home and is only home and able to spend time with the child on Saturday and Sunday, the interviewer should enter 120 (24 hours x 5 days a week) for the number of hours the parent works outside of the home.

10.4.9.3 Coding of the Nine Month Interview

The following questions responses will require coding:
1. Relationship to child, other specify
2. Other, Specify persons living with child
9a. and 10a. First Language of female and male caretakers
9b. 10b. Country of birth of female and male caretaker
14. Other pet not on list, specify
15. Other farm animal not on list, specify

Study staff should assure any responses are legible. Study staff should be familiar with coding methods and ask any questions necessary to assure accurate coding of responses.

10.4.10. Update form for Primary Caretaker Interview (data originally collected in the 9 month Primary Caretaker Interview Form)

The Update form for Primary Caretaker Interview is designed to be interviewer administered at the child's 21 month, 33 month, 45 month, 54 month, 6.5 year clinic visits and every two years thereafter. The purpose of this form is to capture data that has changed since the 9 month Interview form was completed, so this form asks the same questions as the 9 month Interview. This structured interview is completed with the primary caretaker (mother, father or other). Sites have the ability to enter a second form for situations in which the parents are separated/divorced and the TEDDY child lives with one parent part of the time and the other parent the other part of the time.

10.4.10.1. Content Areas of the Update form for Primary Caretaker Interview

Same as the 9 month Interview - see section 10.4.9.1 for details

10.4.10.2. Administration and Review of the Update form for Primary Caretaker Interview

The interviewer will conduct this structured interview with the mother or primary caretaker at the child's 21 month, 33 month, 45 month, 54 month, 6.5 year clinic visits and every two years thereafter, documenting all answers on the interview form provided.

If the form is not completed at the set study visit by the mother or primary caretaker, the interview may be completed by study staff by telephone interview.

The DCC has programmed the online Update form for Primary Caretaker Interview so that the previous visit's submitted data prepopulates on the currently due update form. If a site is unable to administer an Update form, when the not done reason is entered in the tracking system for that form, the next due Update form after that will then be prepopulated with the last submitted form's data. The data is prepopulated so that the staff member can see the previously submitted data and indicate whether the data has changed or not since the last interview was conducted. The site should print-out the online form and conduct the Update form as a structured interview, marking the parent/primary caretaker's answers on the Teleform version of the form.

> **NOTE**: Due to the prepopulation functionality of this form, sites will NOT be able to upload the data for the Update form as a Teleform. All Update form data must be submitted to the DCC through online data entry.

The only exception to which Update form is prepopulated with the previous form's data is when the Update form is first made available through the TEDDY website by the DCC in February 2010 – at this time the 9 month Interview data will populate on all of the subject's Update forms for Primary Caretaker. Once the site has administered the Update form to the parent/primary caretaker at the next due visit, entered the data from the Update form in the corresponding online form for which the date of the interview falls into the window, then the prepopulation of the later forms will act as described above.

The staff member should complete the interview date, visit location code, TEDDY staff code and visit number at the top of the Update form. Each question on the Update form for Primary Caretaker Interview has the following answer choices: "No Change" and "Change to Information". The "No Change" answer choice should be selected when the prepopulated data for that particular question is still exactly the same answer to the question at the time of the interview. If the "No Change" answer choice is selected the prepopulated data will be saved to the database as the answer for this Update form. A check box has been added to the online form for "No change to every question on this form" and when selected all "No change" options on the form will be selected. The "Change to Information" answer choice should be selected when the prepopulated data for that particular question is not the same answer

to the question at the time of the interview. If the "Change to Information" answer choice is selected the prepopulated data will be removed and the staff member is expected to enter the new data. If an error was made on a previously submitted form, do not correct the error on the current form; the error needs to be corrected on the original form that it was submitted in – please see instructions below for corrections. Please note that in order to save the form it is required that either "No Change" or "Change to Information" be selected for every question. If "Change to Information" is selected it is required for the staff member to enter new data in the corresponding fields in order to save the form.

There are several questions which could have more than one answer and for which the answer submitted on a previous Update form is still applicable in addition to an answer to be entered on the current Update form. For example, for question 2 "Who does the TEDDY child live with? (Mark all that apply)", on a previous Update form the site indicated that the child lives with the mother, but now the family has indicated that the child lives with both the mother and the step-father. For these situations the site must choose the "Change to Information" answer choice and then indicate both the previous answer choice and the new answer choice. So for the example given, the site would mark "Change to Information" and then check both the "Mother" checkbox and the "Step-father" checkbox. This applies to answers for the following questions:

- Question 1: What is your relationship to the TEDDY child?
- Question 2: Who does the TEDDY child live with?
- Question 15: Are there any animals or pets in the TEDDY child's house?
- Question 16: Does the TEDDY child live on a farm with animals or are there animals that live outside of the house?

There is a question which once the data has been submitted, the data will never change. However the DCC has provided the answer choices of "No Change" or "Change to Information" for this question because it may be possible that this data was not able to be previously obtained and the site has now obtained it. For the following question once an answer has been submitted, on every subsequent Update form for Primary Caretaker Interview the site must mark "No Change":

- Question 11: What is the biological father's height?

Since sites have the ability to enter a second form for situations in which the parents are separated/divorced and the TEDDY child lives

with one parent part of the time and the other parent the other part of the time, the staff member should make sure that they are showing the correct prepopulated data to the parent/primary caretaker (for example if the parents are divorced and both the mother and the father submitted a 9 month Interview, the staff member should make sure that he/she is showing the prepopulated Update form with the mother's data to the mother and the prepopulated Update form with the father's data to the father). When two Update Forms are submitted in the same visit for a subject, for example the mother is interviewed for one form and the father is interviewed for the second form, staff members should be sure that when he/she answers "No Change" or "Change to Information" that he/she is answering this by comparing the new answer on the mother's Update form to the answers submitted on the mother's previous form and by comparing the new answer on the father's Update form to the answers submitted on the father's previous form.

> **NOTE**: If this is the first time that a second form is completed in the same visit for a subject, then there will of course be no data prepopulated in the second Update form. For every question that the site is able to obtain data for on the second Update form the site should indicate "Change to Information" and enter the new data. For every question that the site is unable to obtain data for on the second Update form the site should indicate "No Change". For example: One 9 month Interview was submitted that was completed with the mother and the parents were married at the time. At the next visit the parents are now divorced and two Update forms are completed, one with the mother and one with the father. The Update form completed with the mother should be compared to the previous 9 month interview data submitted by the mother. The Update form completed with the father should NOT be compared to the previous 9 month interview data submitted by the mother. Instead for every question on the father's form that the site is able to obtain data for the site should indicate "Change to Information" (no matter what data was indicated on the mother's 9 month interview) and enter the new data. For every question that the site is unable to obtain data for the site should indicate "No Change".

If the parent/caretaker divorces his/her spouse or separates from his/her partner since the 9 month Interview was initially completed or since the last Update form was completed, which changes the household composition, for the following questions the parent/caretaker completing the interview should answer for the parent/caretaker who currently lives in the household that the questionnaire pertains to:

- Question 9a: What is your (her) first language?
- Question 9b: What is your (her) country of birth?
- Question 9c: Is this your (her) first child?
- Question 9d: What is your (her) highest grade or level of schooling completed?
- Question 9e: Do you (she) work outside the home now? (Note: this question was removed from the form in April 2018)
- Question 10a: What is his (partner's) first language?
- Question 10b: What is his (partner's) country of birth?
- Question 10c: Is this his (partner's) first child?
- Question 10d: What is his (partner's) highest grade or level of schooling completed?
- Question 10e: Does he (partner) work outside the home now? (Note: this question was removed from the form in April 2018)
- Question 12: Do you (mother, female primary caretaker) currently smoke?
- Question 12a: If yes, do you (mother, female primary caretaker) smoke in the home?
- Question 12b: If yes, do you (mother, female primary caretaker) smoke in the car?
- Question 13: Does the child's father (or other partner) currently smoke?
- Question 13a: If yes, does he smoke in the home?
- Question 13b: If yes, does he smoke in the car?

How to complete questions 9a-9e, 10a-10e, 12, 12a-12b, 13 and 13a-13b for the following divorce/separation scenarios (this assumes that these questions were answered in a previous version of the form):

1. If father/male caretaker had completed the 9 month interview or previous Update form and he and his spouse/partner lived together at that time with the TEDDY child and now father/male caretaker is completing new Update form, his spouse/partner no longer lives with the family and the father/male caretaker does not have another spouse/partner living in the house with the TEDDY child:
    a. Indicate "Change to Information" for question 9 and indicate "Does not live with mother or female caretaker".
    b. Indicate "Change to Information" for questions 9a-9e and leave all answers to these questions blank.

   c. If you can complete an Update form with the mother/female caretaker that the child also lives with in a separate household then this is where you would indicate the mother/female caretaker's information for questions 9a-9e.
2. If father/male caretaker had completed the 9 month interview or previous Update form and he and his spouse/partner lived together at that time with the TEDDY child and now father/male caretaker is completing new Update form, his spouse/partner no longer lives with the family and father/male caretaker has a new spouse/partner living in the household with the TEDDY child:
   a. Indicate "Change to Information" for questions 9a-9e and enter answers to these questions for the new spouse/partner living in the household with the TEDDY child.
   b. If you can complete an Update form with the mother/female caretaker that the child also lives with in a separate household then this is where you would indicate the mother/female caretaker's information for questions 9a-9e.
3. If mother/female caretaker had completed the 9 month interview or previous Update form and she and her spouse/partner lived together at that time with the TEDDY child and now mother/female caretaker is completing new Update form, her spouse/partner no longer lives with the family and the mother/female caretaker does not have another spouse/partner living in the house with the TEDDY child:
   a. Indicate "Change to Information" for question 10 and indicate "Does not live with father or partner".
   b. Indicate "Change to Information" for questions 10a-10e and leave all answers to these questions blank.
   c. If you can complete an Update form with the father/male caretaker that the child also lives with in a separate household then this is where you would indicate the father/male caretaker's information for questions 10a-10e.
4. If mother/female caretaker had completed the 9 month interview or previous Update form and she and her spouse/partner lived together at that time with the TEDDY child and now mother/female caretaker is completing new Update form, her spouse/partner no longer lives with the family and mother/female caretaker has a new spouse/partner living in the household with the TEDDY child:
   a. Indicate "Change to Information" for questions 10a-10e and enter answers to these questions for the new

spouse/partner living in the household with the TEDDY child.

b. If you can complete an Update form with the father/male caretaker that the child also lives with in a separate household then this is where you would indicate the father/male caretaker's information for questions 10a-10e.

5. If father/male caretaker had completed the 9 month interview or previous Update form and he and his spouse/partner lived together at that time with the TEDDY child and now father/male caretaker is completing new Update form, his spouse/partner no longer lives with the family and the father/male caretaker does not have another spouse/partner living in the house with the TEDDY child:
    a. Indicate "Change to Information" for question 12 and indicate "Not applicable"
    b. Indicate "Change to Information" for questions 12a and 12b and leave them blank.
    c. If you can complete an Update form with the mother/female caretaker that the child also lives with in a separate household then this is where you would indicate the mother/female caretaker's information for questions 12, 12a and 12b.
6. If father/male caretaker had completed the 9 month interview or previous Update form and he and his spouse/partner lived together at that time with the TEDDY child and now father/male caretaker is completing new Update form, his spouse/partner no longer lives with the family and father/male caretaker has a new spouse/partner living in the household with the TEDDY child:
    a. Indicate "Change to Information" for questions 12, 12a and 12b and enter answers to these questions for the new spouse/partner living in the household with the TEDDY child.
    b. If you can complete an Update form with the mother/female caretaker that the child also lives with in a separate household then this is where you would indicate the mother/female caretaker's information for questions 12, 12a and 12b.
7. If mother/female caretaker had completed the 9 month interview or previous Update form and she and her spouse/partner lived together at that time with the TEDDY child and now mother/female caretaker is completing new Update form, her spouse/partner no longer lives with the family and the mother/female caretaker does not have another spouse/partner living in the house with the TEDDY child:

   a. Indicate "Change to Information" for question 13 and indicate “Not applicable”
   b. Indicate "Change to Information" for questions 13a and 13b and leave them blank.
   c. If you can complete an Update form with the father/male caretaker that the child also lives with in a separate household then this is where you would indicate the father/male caretaker’s information for questions 13, 13a and 13b.
8. If mother/female caretaker had completed the 9 month interview or previous Update form and she and her spouse/partner lived together at that time with the TEDDY child and now mother/female caretaker is completing new Update form, her spouse/partner no longer lives with the family and mother/female caretaker has a new spouse/partner living in the household with the TEDDY child:
   a. Indicate "Change to Information" for questions 13, 13a and 13b and enter answers to these questions for the new spouse/partner living in the household with the TEDDY child.
   b. If you can complete an Update form with the father/male caretaker that the child also lives with in a separate household then this is where you would indicate the father/male caretaker’s information for questions 13, 13a and 13b.

If the site needs to make a correction to a submitted form, if the data for the next Update form has not been submitted to the DCC yet, then the site can go in to the form that they need to make the change on and update the data. For example, if the site has submitted the 21 month Update form to the DCC, but has not yet submitted the 33 month Update form to the DCC and needs to make a correction on the 21 month Update form, the site can go into the 21 month Update form and make the change. If the site needs to make a correction to a submitted form, but the data for the next Update form has already been submitted to the DCC, then the site should NOT make the correction to the form and should contact the DCC. For example, if the site has submitted a 45 month Update form and a 54 month Update form, but needs to make a correction to the 45 month Update form, the site should not change any data on the 45 month Update form and should instead contact the DCC.

If a 9 month Interview was never completed for the subject, the site should complete the Update form at the next visit. If the 9 month Interview was not collected for a subject, then there will of course be no data prepopulated in the Update form. For every question that the

site is able to obtain data for on the Update form the site should indicate "Change to Information" and enter the new data. For every question that the site is unable to obtain data for on the Update form the site should indicate "No Change".

If on the 9 month Interview or an Update form an answer was not able to be obtained to a question, on the next due Update form there will of course be no data prepopulated in the Update form for that question. For every question that the site is able to obtain data for on the new Update form the site should indicate "Change to Information" and enter the new data. For every question that the site is unable to obtain data for on the new Update form the site should indicate "No Change".

For the question "How many rooms are in your home?" – if the family has remodeled their home since the last completion of this questionnaire that changed the number of rooms in their home, but not the usable square footage/meters of the home, then the site should mark "No Change". If the remodeling of the home changed the number of rooms and added usable square footage/meters then the site should mark "Change to Information" and indicate the new number of rooms in the home.

See section 10.4.9.2 for other administration details that apply to this form.

10.4.10.3. Coding of the Update form for Primary Caretaker Interview

Same as the 9 month Interview - see section 10.4.9.3 for details

10.4.11. Annual Questionnaire

The Annual Questionnaire is designed to be used by multiple respondents: mother, father, and/or primary caretaker. For example, for children with two parents involved in their lives, two annual questionnaires may be completed for each child – one by the mother and one by the father. In some cases, there could be as many as three annual questionnaires (e.g., mother, father, other – stepfather). The Annual Questionnaire will be administered at 15, 27, 39, 48 month visits and annually thereafter through the 14 year visit. At the 15 year visit the End of TEDDY Parent Questionnaire will be administered.

10.4.11.1. Content areas of Annual Questionnaire

The Annual Questionnaire provides information on:

- Respondent perception of the child's risk for TID
- Respondent worry or anxiety about the baby's risk for TID
- Depression assessed by the Bradley Well-Being questionnaire

- Respondent beliefs about whether anything can be done to prevent TID in the child and whether they have done anything to try and prevent T1D in the child
- Anything done to monitor the child's risk of developing T1D
- Respondent reactions to study participation

Actions Done to Prevent Child from Developing T1D (question number 9) versus Things Done to Monitor Child's Risk of Developing T1D (question number 10)

Actions Done to Prevent Child from Developing T1D refers to behaviors designed to actually prevent the disease. Monitoring refers to early detection of the disease while prevention refers to activities designed to stop the disease from occurring. Examples might include changing the child's diet, avoiding sweets, breastfeeding, trying to protect the child from infections. It is possible that some parents view participating in TEDDY as a prevention activity because their child may be eligible for a prevention trial should the environmental trigger(s) for TID be identified. However, TEDDY itself is not a prevention trial.

Occasionally a parent may indicate a monitoring behavior as a prevention behavior. When this happens try to have a clarifying conversation with the parent in order to code this properly under the "Things Done to Monitor Child's Risk of Developing T1D" question. If it is not possible to have this conversation this can be coded under the "Actions Done to Prevent Child from Developing T1D" question; the specific code request should be sent to the DCC who will then discuss it with the Psychosocial Committee.

Things Done to Monitor Child's Risk of Developing T1D refers to efforts to detect diabetes in the at-risk child. Common activities might include watching the child for symptoms of diabetes – frequent urination, drinking a lot, fatigue. Sometimes parents will test the child's blood or urine for evidence of glucose. Other times they might take the child to the doctor more often. For many parents, participating in TEDDY may be viewed as a way to monitor the child for diabetes. Because the child is being tested frequently, the parent might expect the child's diabetes to be detected early.

When parents describe a behavior as a monitoring or prevention behavior, be sure to ask questions for clarification. For example, if a mother says she is making sure her child "eats healthy" to prevent diabetes, ask her what she means by that. Her response will make it easier to code her behavior into the correct category.

For example, she might say that she limits her child's sugar or she might say she is feeding her child only organic foods or that she is avoiding additives or that she is making sure her child eats lots of vegetables. All of these responses are examples of what someone might mean by "eating healthy." However, if you don't get further clarification, you haven't really captured what kinds of behaviors she is engaging in.

If someone says participating in the TEDDY study is how they are monitoring or preventing the child's diabetes, be sure to ask for clarification. Parents may view TEDDY participation in many different ways and we need to understand each parent's perspective in order to code the response accurately.

If a parent/caretaker lists more than one action to prevent or thing done to monitor Type 1 Diabetes that falls under the same "Other" code (AP080-Other not specified elsewhere, TM11-Other monitoring behavior not previously specified, etc.) the staff member should indicate the corresponding code on the form for each behavior listed. For example, if the parent/caretaker indicates three actions that fall under code AP080, then the staff member should indicate code AP080 three times on the form.

Occasionally a parent may indicate a prevention behavior as a monitoring behavior. When this happens try to have a clarifying conversation with the parent in order to code this properly under the "Actions Done to Prevent Child from Developing T1D" question. If it is not possible to have this conversation this can be coded under the "Things Done to Monitor Child's Risk of Developing T1D" question; the specific code request should be sent to the DCC who will then discuss it with the Psychosocial Committee.

10.4.11.2. Administration and Review of the Annual Questionnaire

The Annual Questionnaire is completed at the 15, 27, 39, 48 month study visits and every year thereafter through the 14 year visit; at the 15 year visit the End of TEDDY Parent Questionnaire will be administered. The questionnaire is completed by the mother or primary caretaker and by participating fathers. The Clinical Center also has the option of sending the Annual Questionnaire(s) home to the mother or primary caretaker and Father (if applicable), to be completed prior to the annual visit and to be brought in with them to their scheduled appointment. The respondent should be provided with the Instruction Sheet and a black pen.

If the Annual Questionnaire is not completed at the appropriate visit (15, 27, 39 etc month visit), it may be mailed home for completion, with appropriate instructions and an addressed stamped return envelope. If the questionnaire is not completed and returned in a timely manner, the questionnaire may be completed by study staff by telephone interview.

Study staff should review all completed questionnaires to assure that all item responses are clear and none are accidentally skipped. In the US, assure the date of questionnaire completion is entered correctly: day, month, and year.

Since the Annual Questionnaire is repeated, study staff should indicate the timing of each Annual Questionnaire (i.e., 15, 27, 39, 48 months, years 5-14) in the "Office Use Only" box at the end of the questionnaire.

Per the Psychosocial Committee the response to "Below, please tell us anything else you would like us to know about your experience with TEDDY" in the End of TEDDY Parent Questionnaire will not be translated or coded.

10.4.11.3. Coding of the Annual Questionnaire

The mother or primary caretaker may write in responses to the following questions:

Q2: relationship to child is other, specify
Q9. kinds of things that done to try and stop or prevent diabetes in child
Q10. done anything to monitor or keep an eye on child's risk of developing diabetes

Study staff should assure any responses are legible. Study staff should be familiar with coding methods and ask any questions necessary to assure accurate coding of responses.

10.4.12 Child Behavior Checklist

The Child Behavior Checklist (CBCL) is a well-validated instrument that has been used extensively worldwide for over 25 years. The CBCL is translated into all TEDDY languages. It is a measure of child behavior from which five DSM-oriented scales can be obtained. The scales consist of two scales measuring internalizing behaviors (affective problems and anxiety problems), two scales measuring externalizing behaviors (attention deficit/hyperactivity problems, and oppositional defiant behavior) and one scale assessing pervasive developmental problems.

The CBCL consists of both closed-ended questions and open-ended questions that provide the opportunity for the parent to describe the child's problems and strengths. In the TEDDY CBCL, all open ended questions have been deleted and only the parents' response to the 99 closed-ended questions are recorded. The TEDDY CBCL is available in the Teleform format in all languages.

The child's primary caretaker should complete the CBCL on an annual basis when the child is 3.5, 4.5 and 5.5 years of age. Usually, the person completing the CBCL will be the child's mother but if someone else is the child's primary caretaker (e.g. grandmother or father) that person should complete the CBCL. TEDDY staff will be very familiar with who is the child's primary caretaker, since the child will have been in TEDDY for > 3 years. Usually this is the person who brings the child to the TEDDY visit. Note that the mother is the "primary caretaker" even if the child spends a lot of time in day care or someone else's care because the mom works. A father would be the primary caretaker if he stays home with the child when the mother works or if he is a single parent. If a child lives with his or her grandmother, then the grandmother would be the primary caretaker who should complete the form. TEDDY staff should identify who is the child's primary caretaker and give or send the CBCL to that person. If both parents care for the child equally, either parent can complete the form. If both parents want to complete the form, they should be asked to complete it together.

Preferably the CBCL should be completed by the parent or primary caretaker at home shortly before the 42, 54 and 66 month clinic visits when the saliva for the cortisol measurement also is collected. Although this is the preferred timing of these two data collection elements for those sites collecting both elements, the CBCL will be accepted in a year-long window and it is not required to be in conjunction with the cortisol measure. The window for the 3.5 year data collection is any time during the child's third year. Similarly, the window for the 4.5 year data collection is any time during the child's fourth year and the window for the 5.5 year data collection is any time during the child's fifth year.

The CBCL form can either be given to the parent (primary caretaker) at the visit preceding the 42, 54 and 66 month visits or sent home by mail before the visit. If the CBCL is given out at the previous visit, a reminder card should be sent home or a reminder call given prior to the upcoming visit. This is especially important for the 54 and 66 month visits as the clinic visits are done only twice a year when the child reaches 4 years of age. Ideally the parent would bring the completed form to the scheduled visit.

Should a parent forget to fill out the CBCL in advance of the visit, the CBCL can be filled out at the visit. If the CBCL is completed at a study

visit, completion before the child's blood draw is preferred. However, CBCL completion any time during the visit is acceptable.

Should any of the 42, 54 or 66 month visits be missed, the CBCL should be sent home together with an addressed and prepaid envelope. If it is not possible to have the CBCL completed at the corresponding visit or mailed and sent back to the clinic, the CBCL can be collected at the next visit or by phone.

After the CBCL has been filled in, the form should be checked for completeness preferably at the clinic visit. If there are omissions, if possible, the person who filled in the form should be asked to make it complete. A follow-up telephone call may be used to complete missing items or to clarify responses. When the CBCL is completed, TEDDY staff should indicate where the form was completed (at home; in clinic before the blood draw; in clinic after the blood draw; by telephone) on the form. If two methods were used (home completion plus follow-up telephone call to complete a missing item), TEDDY staff should indicate the location where most of the items were completed ("at home" in the above example). CBCL data should be transmitted to the DCC through scanning and uploading of the Teleform (see MOO section 17.2.5. and 17.2.6. for instructions) or through online data entry.

The DCC will score the CBCL and inform the site of each child's results. Results sent by the DCC will indicate whether the child scored within or above the normal range for externalizing behaviors and internalizing behaviors; no scores will be provided. If a child scores above the normal range, suggested wording for explaining this to the child's parent will be provided as part of the DCC's report.

At the child's next study visit, parents can be informed of the CBCL results. However, if the child has one or more scores above the normal range and the child is on an every 6 month study visit schedule, TEDDY staff should call the parent and discuss the child's results. Any parent who calls for the results between study visits, should be informed of those results.

NOTE: Even if this is the second or third time that a CBCL has been conducted on the child with the child having one or more scores above the normal range, the parent should be notified of the results each time. The reasoning behind this is:

1. The CBCL is given annually and if a child remains high on the CBCL – even if in treatment – the parent should be told.
2. It could be quite difficult to ascertain whether a child is in treatment or has received treatment. Perhaps the child went only one time and never returned. It would be too time consuming for staff to ascertain

the nature and quality of any treatment the child received. Consequently, informing the parent of a second (or third) high score could be useful to the parent (perhaps the parent will return to treatment, discuss with current therapist, or consider alternative treatment).

3. If the parent has the child in treatment and expresses concern about the high score, the TEDDY staff member can suggest the parent discuss the high score with the child's therapist. TEDDY staff should remind the parent that "It is important to remember that the CBCL is an assessment tool. It does not provide a formal psychiatric diagnosis."

It is important to remember that the CBCL is an assessment tool. It does not provide a formal psychiatric diagnosis. Rather, high scores suggest that the child should be referred to a mental health professional for further diagnostic work-up and treatment, if appropriate. Each site should have a referral plan to assist parents whose children have CBCL scores above the normal range. All referrals should be indicated in the appropriate place on the Physical Exam form.

10.4.12.1 Scoring of the Child Behavior Checklist

Once a site has submitted the Child Behavior Checklist data to the DCC (either through direct online data entry or through the Teleforms system) the CBCL will be scored by an automatic scoring system. The corresponding site will receive one of the following three types of automatic emails:

1) <u>If data is missing for less than 8 questions</u>: Site will receive an automatic email containing the following information.

I. <u>Externalizing Behaviors</u>:

- Either normal or high will be indicated
  - If high, the email will contain the following suggested wording:

    We have received your child's scores on the Child Behavior Checklist. These scores suggest your child may be more active than other children the same age. Or your child may be more difficult to manage than other children the same age. This does not mean your child definitely has a behavior problem. But we think taking your child to a behavior specialist could be helpful.

II. <u>Internalizing Behaviors</u>:

- Either normal or high will be indicated
  - If high, the email will contain the following suggested wording:

    We have received your child's scores on the Child Behavior Checklist. These scores suggest your child may be unhappy compared to other children the same age. Or your child may be more worried than other children the same age. This does not mean your child definitely has a behavior problem. But we think taking your child to a behavior specialist could be helpful.

2) If data is missing for 8-20 questions: Site will receive an automatic email containing the information listed under number 1 above and the email will state: "Profile is of questionable validity due to N unanswered questions."

3) If data is missing for greater than 20 questions: Site will receive an automatic email stating: "Profile was not scored due to N unanswered questions."

If a site should edit CBCL data that has been submitted to the DCC, the CBCL will be automatically rescored and one of the 3 types of emails described above will be generated and emailed to the corresponding site. The email will indicate in the subject line "TEDDY CBCL Results Notification - Form rescored because submitted data has been revised".

10.4.13 Self-assessment Pubertal Status Instruments

Many children progress to type 1 diabetes (T1D) during puberty but little is known about the potential effects of puberty on autoantibody seroconversion. The TEDDY cohort provides a unique opportunity to prospectively follow children with known genetic risk for T1D through the development of puberty in order to definitively answer questions regarding the effects of androgens and estrogens on diabetes risk.

Specific Aim: To determine if pubertal progression is associated with augmentation in risk for autoantibody seroconversion or development of T1D amongst children in the TEDDY cohort.

Hypothesis 1: Initiation of puberty is associated with an increased risk of seroconversion from negative to positive.

Hypothesis 2: Initiation of puberty is associated with an increased risk of transitioning from single antibody to multiple antibody positivity.

Hypothesis 3: Initiation of puberty is associated with an increased risk of developing T1D.

Therefore TEDDY will use self-assessment pubertal status instruments every 6 months for TEDDY visits beginning at age 8 years and until pubertal status is assessed as Stage 5 for both pubic hair and breast development/genitalia or the child reaches 15 years of age. Self-assessment may be done at the TEDDY clinic during the visit or at home before the visit. The form is available to be completed on paper or through the TEDDY Portal. The self-assessment can be made by the parent, by the child or the parent and child can complete the assessment together. If there is a disagreement between the parent and child on which stage of puberty the child is in, the parent's assessment should be used up until the child is 10 years of age. At 10 years of age and beyond if there is a disagreement between the parent and child on which stage of puberty the child is in, the child's assessment should be used.

The gender version of the form that will display on the Participant's Details Page will be based on the gender entered on the subject's Screening Form.

Once "yes" and a date has been entered for the question "Have you started your period?" on the female form the date will be prepopulated and locked on all future online forms. For data submissions through Teleforms, the Teleforms processor has been programmed to search for an existing date in the database and if it finds one, the system will ignore the date entered on the current Teleform; if the processor does not find a date in the system it will insert the date from the current Teleform into the database.

The Participant's Details Page has been programmed so that once stage 5 is answered for both breast development and pubic hair development on the female form or stage 5 is answered for pubic hair development on the male form, the form will not be expected at future visits and will not display on the Participant's Details Page for future visits. If stage 5 is answered for both breast development and pubic hair development on the female form, but the subject has not started her period yet, the form continues to display at future visits so that we can capture the start date of the period. Once the start date of the period has been entered, the form will not display at future visits.

10.4.14Child-Report Questionnaires

10.4.14.1 Timeline of Questionnaire Administration

Item/ Questionnaire	Prior to 10 yr visit	10 yr	10.5 yr	11 yr	11.5 yr	12 yr	12.5 yr	13 yr	13.5 yr	14 yr	14.5 yr	15 yr
Junior Scientist (JS) Book #3	X											
Annual Child Questionnaire* through 14 year visit; at 15 year visit End of TEDDY Child Questionnaire		X		X		X		X		X		X
Child Stressful Life Events (CLE) Scale** (in TEDDY Book)		X	X	X	X	X	X	X	X	X	X	X
Strengths and Difficulties Questionnaire (SDQ)***					X				X			

*For the 10-year administration, the questionnaire will be slightly different and will be called the "First Child Questionnaire". The First Child Questionnaire will include items about the JS Book #3 and will include the full version of the STAI (20 items) up until January 2017 when the STAI was shortened to 6 items. Subsequent administrations of the Annual Child Questionnaire will not include the JS Book #3 items and will include a shortened version of the STAI (the shortened STAI was available in January 2017, up until that time the 20 item STAI was administered through the Annual Child Questionnaire).

**Children who have been deemed persistent autoantibody positive will remain on the 3 month visit schedule after four years of age; for these children the "Child Stressful Life Events Scale" will be completed every 3 months.

***To be completed by both the child and the parent.

10.4.14.2 Preparation of Children

TEDDY staff members have engaged in a variety of child-focused tasks to help ensure child comprehension of their role on the project. Additionally, in the US, children have provided assent to participate in TEDDY beginning at age 7. The assent process included explanations of TEDDY purposes and procedures. At age 10, most US sites will also require a more formal, written assent process.

Junior Scientist materials

TEDDY has developed a standardized method of informing children across sites about important TEDDY/research concepts, which includes primarily the Will & Emma/Junior Scientist books. This series of three books has been designed to increasingly inform the TEDDY children of their role on TEDDY, the purpose of the project, and their increased risk for diabetes.

At the 9.5-year visit, staff should have a discussion with parents and children regarding the upcoming JS book #3 and the associated questionnaires that the child will complete at their next visit. In the US, staff can also briefly introduce the more formal assent process, which will occur at the 10-year visit. Staff should emphasize the importance of the child and parent reading the JS book #3 in order to be prepared to complete child questionnaires.

Prior to the 10-year visit, children should receive the final Junior Scientist book #3. At most sites, staff will send out the Junior Scientist book #3 by mail 3-4 weeks before the 10 year visit together with an information letter to the child. The child information letter (see Appendix F) will contain the aim(s) of the Junior Scientist book #3 and information about the questionnaire administration at the next visit. The letter will also encourage the child and the parent(s) to read the Junior Scientist book #3 before the visit. When reasonable, staff should remind the family the week before the 10-year visit about the importance of reading the JS book #3 (by phone, email, or mailed postcard). Some sites may need to revise this protocol to accommodate site-specific issues. Regardless of the method and timing of delivery, it is important that families receive the JS book and a brief explanation of the child questionnaires prior to the 10-year visit.

Although it is strongly preferred that children have read the Junior Scientist book #3 to have a thorough understanding of

TEDDY, children who have not done this will still be given the child-report questionnaires. Parents may feel more comfortable reading the questionnaires prior to their child completing them and staff can provide the questionnaires to the parents to read over. As with all TEDDY tasks, either parents or the child may opt out of the child questionnaires if they desire.

10.4.14.3 Administration of Questionnaires

10.4.14.3.1 General Considerations

It is important that the administration of child self-report questionnaires focus on 1) ensuring that the child understands the questions presented to them and 2) ensuring that the child can provide accurate and honest responses without leading prompts by parents or staff members. Preference should be given to children reading questionnaires independently rather than having staff or parents read items to them. If children have reading difficulties, staff (rather than parents) should read items to children without using a leading tone/emphasis. In all cases, staff and parents should refrain from commenting on the children's responses. In order to help both parents and children feel more comfortable, it may be useful to allow parents to independently read the questionnaires prior to the children answering items; however, parents should refrain from reading or helping the child with their responses during administration.

10.4.14.3.2 First Administration

The first administration of the child questionnaires (at the 10-year visit if family is compliant with study protocol; if the subject misses the entire window for the 10 year visit, then the 11 year visit forms will be the first administration of the child questionnaires) should be completed in clinic (unless on Long-Distance Protocol (LDP)) in order to ensure understanding and proper completion. It is also preferred that the questionnaire be completed in clinic after the first administration when possible, although individual family and clinic circumstances may dictate that alternative administration methods be used (e.g., online forms via the TEDDY portal, hard copies of forms mailed, emailed forms (CLE list).

NOTE: TEDDY is restricted from emailing the First Child Questionnaire and Annual Child Questionnaire and End of TEDDY Questionnaire due to STAI copyright rules, as well as the SDQ, therefore sites should not email these questionnaires to the subjects.

When administering the questionnaire for the first time, the following points should be included in an age appropriate script, for both parents and children (see Appendix G for script):

1) The purpose of the First Child Questionnaire is to measure the impact of TEDDY participation and T1D screening. This will include a measure of child anxiety about T1D, perception of T1D risk, and behavioral changes made due to TEDDY participation.
2) The First Child Questionnaire will also collect information on child satisfaction with TEDDY. This is important to the study because child satisfaction has been linked with retention and compliance for TEDDY parents.
3) It is thought that asking the TEDDY children about their own attitudes, views, and feelings, and thus inviting them to be more active participants may constitute a potentially important retention tool in TEDDY.
4) Ethically, we are required to inform children who are participating in medical research (i.e., assent) and to ensure they understand the information provided.

10.4.14.3.3 In-Clinic Administration Guidelines

1) An Instruction Sheet (see Appendix H for instruction sheet) should be included with all questionnaires.
2) If possible, a black ink pen should be provided for completing the questionnaires.
3) If children do not understand the wording of a question on the full, 20-item version of the STAI, they can be told to skip that item. Staff should not provide an explanation or definition of the item.

4) Staff may provide very basic clarifications (e.g., reading a difficult word, saying "this is asking about what you think about the Junior Scientist book you received in the mail") of other items but should refrain from fully explaining items. In order to minimize guessing or random answering, children should be instructed to skip an item if they do not understand the item.

10.4.14.3.4 Tracking System "Not Done" Reason for Child First and Annual/End Questionnaires and SDQs

When any of the First or Annual Child Questionnaires or End of TEDDY Child Questionnaire or SDQs are not completed, staff should indicate the reason the form was not done in the tracking system. Most of these choices are used for all other parent report forms (i.e., 1-6); however, one new choice has been added for the child report forms (i.e., 7) and an explanation is included below. Choices are as follows:

1) Unable to contact subject
2) Parent refused
3) Missed appointment
4) Illness
5) Other
6) Child Refused
7) Child developmentally unable (ONLY available in the First and Annual Child Questionnaires' and End of TEDDY Child Questionnaire and Child SDQ's tracking system; this choice should be used by staff when child has a diagnosed condition such as mental retardation or autism that impacts their ability to complete the First/Annual/End of TEDDY Child Questionnaire or SDQ. When parents state that they believe their child is "not mature enough" or "not ready" to complete the First/Annual/End of TEDDY Child Questionnaire or SDQ at a particular visit, this should be indicated as "Parent refused")

10.4.14.3.5 Questionnaire-Specific Guidelines

Annual Child Questionnaire. The Annual Child Questionnaire administration will begin at age 10 and will be administered yearly thereafter through the 14

year visit and then the End of TEDDY Child Questionnaire will be administered at the 15 year visit (see Timeline above). The Annual Child Questionnaire will have an instruction sheet attached on top giving simple and clear instructions and emphasizing that the child should fill out the questionnaire alone and without assistance from the parents.

The first administration of the Annual Child Questionnaire will be slightly different and will be called the "First Child Questionnaire". The First Child Questionnaire will include items about the JS Book #3 and will include the full version of the STAI (20 items). Subsequent administrations of the Annual Child Questionnaire will not include the JS Book #3 items and will include a shortened version of the STAI.

Until approximately December 2015, the First Child Questionnaire will contain the full 20-item version of the STAI. This full version will be given to allow the Psychosocial committee to conduct an item analysis, retaining only the best 6-8 items in subsequent administrations. While the STAI is standardized for children as young as 8 years old, some children may have difficulty understanding the words on the STAI. In these cases, staff should ensure that the difficulty is not due to a reading challenge (e.g., they should read the item to the child). If the child continues to have difficulty understanding the item, staff should instruct the child to skip the item. Staff explanations or definitions of STAI words should not be given. After December 2015, a shortened version of the STAI will be used on the First Child Questionnaire and all subsequent administrations of the Annual/End of TEDDY Child Questionnaire.

Per the Psychosocial Committee the response to "Please tell us anything else you would like us to know about your experience with TEDDY" in the End of TEDDY Child Questionnaire will not be translated or coded.

Child Life Events List. The administration of the CLE list will be very similar to the parent-completed LE list and will be given at every visit beginning at age 10 (i.e., twice a year for autoantibody negative families, four times a year for children who have been deemed

persistent autoantibody positive). In clinic, a two-page CLE list will be given to the child to review. A cover sheet giving short, clear instructions for the CLE interview process should be stapled on top. Children will be instructed to carefully read over the list and circle any events that have occurred since their last TEDDY visit. Staff will then ask the child to state the events they have circled or to state the corresponding letter. Staff will then follow-up with a question about the impact of the event. Children should complete the CLE list without input from their parent.

Strengths and Difficulties Questionnaire (SDQ). The SDQ is a screening measure of general child psychological/behavioral functioning. It measures similar domains to the CBCL and is replacing that questionnaire. At the 11.5-year and 13.5-year visit, both the parent(s) and child will complete the SDQ independently. The parent(s) and child should be given instruction by the TEDDY interviewer utilizing a script (See Appendix K). The parent(s) and child should be instructed to fill out the questionnaires separately. If two parents will be able to complete the SDQ, they should each complete their own questionnaire (rather than completing one questionnaire together). It is preferred that the first SDQ administration take place in clinic (except for LDP families). However, in challenging circumstances (e.g., not enough time during the clinic visit), it is acceptable to complete the SDQ at home or through the TEDDY Portal, even for the first administration. If this occurs, staff should discuss the SDQ in-person or by phone with the family to ensure understanding the purpose of the SDQ, administration, and follow-up notification procedures.

Some children may have difficulty understanding the words on the SDQ, although it is standardized for use with children at the age of 11 years. In these cases, staff should ensure that the difficulty is not due to a reading challenge (e.g., they should read the item to the child). If the child continues to have difficulty understanding the item, staff should instruct the child to skip the item.

After the SDQ forms are entered by staff through the TEDDY website, an automatic email will notify staff

when child and/or parent responses suggest that the child has clinically significant difficulties measured by the SDQ (i.e., Internalizing or Externalizing problems), staff will then contact the child's parent to inform them of this elevation and provide local resources. This process will be analogous to the CBCL notification system (see section 10.4.14.7 for description and procedure related to the notification system)

10.4.14.4 Review of Questionnaires

It is important to review all child-administered questionnaires during the clinic visit in order to assure:

- The questionnaire is completed in black pen
- Any questions the respondent may have are answered
- The date the form was completed by the respondent
- For skipped items: Study staff will inquire whether this was a purposeful or accidently skipped item.
  - Staff will ensure that accidentally skipped items are completed.
  - However, skipped items are permissible if a) the child refuses to respond to an item, or b) the child reports significant difficulty understanding an item (even after the item has been read out loud by staff).
  - If a respondent purposefully refuses an item, the reviewer will so note on the questionnaire and initial and date
    - For the STAI items a "Not done" radio button has been provided on the online form for each item for the TEDDY study staff member to indicate that the child did not answer the question
- The respondent's answer is clear if a response to an item has been changed. If an answer is changed:
  - A large X should be drawn across the incorrect response, the respondent should initial and date next to it and the new answer should be clearly indicated
- The respondent has not filled in boxes designed for staff coding.
- All dates are written using the European format (day/month/year)

10.4.14.5 Long-Distance Protocol Administration

For the administration of the First Child Questionnaire, at the 10-year visit, it is highly suggested, but not required, that the

children be present via phone to receive instructions on form completion (see Appendix G for script). Staff should also plan to provide instructions via phone to children directly at the 11.5-year visit, when they will receive the SDQ instrument for the first time. At other visits, it is recommended that staff speak directly to children via phone to answer any questions; however, this may not always be feasible given time/scheduling constraints. When it is not possible for the child to be present during the phone interview, the parent should be instructed utilizing the script. However, if staff cannot interview the child via phone, the child cannot complete the CLE list, due to the necessity of staff querying each reported life event. If this occurs, please select the "Not Done" radio button on the Child Life Experiences for child reporting question on the teleform and online TEDDY Book Data Extraction Form.

All child questionnaires will have a separate, preceding instruction sheet attached giving simple and clear instructions emphasizing that the child should fill out the questionnaire alone and without assistance from the parents. When it is not possible for staff to speak directly with LDP children via phone prior to questionnaire completion, the parent should ask the child to read the instruction before asking to child to complete the questionnaire(s). Again, the CLE list cannot be completed without interviewing the child, thus the family should be instructed to skip this form if the child cannot be reached directly by phone.

Child Life Events List: LDP guidelines. While the administration of the Annual Child Questionnaire and the SDQ will be generally equivalent for LDP children, the Child Life Events list may require variations in administration for those on the LDP. The CLE list should be mailed out ahead of the phone interview for the child to review. A cover sheet giving short, clear instructions for the CLE list process should be stapled on top. During the phone interview, the TEDDY interviewer can ask the child to state the event(s) they have circled by reading them or providing the corresponding letter. Staff will then follow-up with a question about the impact of the event. If the child cannot be reached directly by phone, the CLE list will not be completed and staff should select the "Not Done" radio button on the Child Life Experiences for child reporting question on the teleform and online TEDDY Book Data Extraction Form. We will re-evaluate the staff and family burden of speaking directly with the child by phone to gather these data in December 2015.

Once the child has completed the questionnaires, staff should follow review of questionnaire guidelines (see Review of Child Questionnaires section above).

10.4.14.6 Out of Clinic Administration

Preferably, children not on LDP will complete child questionnaires during a study visit in clinic. However, for some families scheduling lengthy TEDDY visits may be problematic. Following the first administration of questionnaires at 10 years of age, which is required to occur in clinic (unless on LDP), staff may send questionnaires home to be completed before or after subsequent visits if needed. Annual Child Questionnaires and SDQs may also be completed on the TEDDY portal. Some forms can be emailed (CLE list); however, due to copyright restrictions on the STAI items, the First/Annual/End of TEDDY Child cannot be sent via email. The SDQ can also not be sent via email.

When the appointment for the next TEDDY visit is being scheduled with the family and it becomes clear that time does not permit completing the child questionnaires during the visit, families should be provided with the questionnaires before the next visit. Alternatively, sites can mail questionnaires in preparation for a visit or can direct families to the TEDDY portal to complete questionnaires online.

Instruction to parents and children. Before providing respective questionnaires to families, in order to avoid bias, parents will be instructed by the study staff on the importance of the child independently answering the questionnaires. If a child has difficulty reading items on the questionnaires, parents should be instructed to contact study staff to read difficult items via phone or during the next visit. Additionally, parents should be instructed to have the child skip difficult items and study staff can follow-up with the child by phone or in clinic if needed. The parent may help filling in the date or other basic information on the questionnaire.

Administration of questionnaires. In general, the child questionnaires will be provided to the families 2 to 4 weeks in advance of the upcoming scheduled TEDDY study visit, although site-specific protocols are permissible. If the appointment was scheduled at the last clinic visit, study staff should remind parents of the questionnaires by phone before sending the questionnaires. If the appointment is scheduled by

phone, parents should be instructed on the telephone and questionnaires can be sent in after the phone call. The family can choose from three options for how the child prefers to complete the questionnaires: (1) hard copies, (2) online through the TEDDY portal for the Annual Child Questionnaire, SDQ and End of TEDDY Child Questionnaire or (3) electronically by email for the CLE list (not permitted for the First/Annual/ End of TEDDY Child Questionnaire and SDQ). The study staff will then provide the access to the preferred questionnaire version.

When the child has completed the questionnaire, the family and/or child will be asked to bring the completed forms to the study visit in clinic, if applicable. Study staff will check for completeness of the form in clinic, on the TEDDY portal, or by phone, as applicable (see Review of Child Questionnaires section above).

10.4.14.7 SDQ Notification System

After the parent(s) and child have completed the SDQ, staff should enter data into the TEDDY members website as soon as possible to allow for the questionnaire to be scored. It is preferred that staff enter all available SDQ forms at the same time, to avoid multiple email notifications. However, it is acceptable to wait up to one month to enter SDQ data if staff expects that additional SDQ forms will be obtained. For example, if one parent will complete the SDQ at home after the clinic visit, staff can wait up to one month to enter all SDQ forms. The notification system will calculate scores every 48 hours using data from all available parent and/or child questionnaires that have been entered. For example, if only one SDQ questionnaire is entered, the notification email will include scores from only one SDQ. If staff subsequently enters another SDQ form after the 48 hour window in which scores are automatically calculated a second email will be sent that includes both the new form data and the previously entered data. This second email will contain language to indicate that additional data has been added (e.g., *scores revised due to revised/additional data*)

While the SDQ can provide scores on 5 domains, we will only be reporting score elevations based on *Internalizing* (e.g,.mood problems such as depression or anxiety) and *Externalizing* (e.g., behavior problems such as arguing or breaking rules) scales. This is analogous to the reporting for the CBCL. Once SDQ data

is entered, an email notification will be sent to the designated study staff at that site. There are three possible notifications:

1) *Not elevated* (child does not show significant elevations on the SDQ scale)
2) *Very high* (child's scores is clinically elevated on the Internalizing scale, Externalizing scale, or both)
3) *Not able to calculate scores due to missing responses* (neither the parent nor child completed enough items to calculate a score; at least 60% of items on a scale must be completed to calculate a score).

When a child's Internalizing and/or Externalizing scale is elevated, the notification email to staff will include a script for discussing the elevation with the family (see Appendix K). It is preferred that staff discuss elevations with the family by phone and provide a follow-up letter/email. However, there may be slight site-specific variations in this procedure. In all cases, parents should be informed that SDQ is a screening instrument only and that elevations should be further evaluated by a health or mental health professional. The type of elevation (i.e., Internalizing versus Externalizing) does not change the evaluation/referral recommendation. Each site has a prepared list of referrals/resources that families can use to obtain follow-up evaluation and care (e.g., psychologists, pediatrician, nurse case managers). In addition to typically providing referrals by phone, all sites should provide a printed list of referrals by mail/email or in person. Based on CBCL data, we expect less than 2% of the TEDDY cohort to have an elevated score on the SDQ scales.

Please note, staff will not be given information about the reporter (i.e., parent versus child) that led to the elevation. For example, if a child's responses were elevated on the Internalizing scale, but the parents were in the normal range, the family will be notified only of an Internalizing elevation, not of the differences in the child versus the parent report. Staff can explain to families that parent and child responses are aggregated and are not kept separately for the purposes of reporting. Staff should direct any questions or challenges with family notification to the Psychosocial Committee and they can be discussed on an individual basis.

10.4.15 Parent Experiences Questionnaire/Child Experiences Questionnaire

The Parent Experiences Questionnaires and Child Experiences Questionnaire (if the child is at least 10 years of age) should be given to all

families that are no longer participating in TEDDY, including those whose child develops diabetes or who choose to withdraw because their child's HLA additional genotyping results differ from the HLA screening results - making the child not eligible for the study. See MOO section 8.3.5 and MOO section 8.3.5.2. for details about the Parent Experiences Questionnaire/Child Experiences Questionnaire.

10.5 General Training Requirements

Study personnel who are administering the interview material covered in this section are required to complete the following steps:

- Review of this chapter of the manual of operations and all others that are applicable to their work.
- Participate in either a centralized training session or review the training video for those portions of the interview protocol that they will be conducting.
- Review all questionnaires with senior clinical coordinators to review any local administration issues, questions, probes and to provide insight into how the interview works in practice.
- Each local center will monitor each interviewer's readiness for data collection with participants. A recommended sequence of practice and mock sessions is:
    - Each interview should be demonstrated to the new interviewer by a trained clinical staff person (this is a good idea even if they were demonstrated in the training interview).
    - Each interview should be practiced 3 times with non-participants, so that new personnel are familiar with the interview and identify questions they may have about its administration.
    - When the interviewer is ready, mock interviews with 2 trained clinical staff persons, one role playing a "real patient" and one observing should be conducted. The number of these mock sessions needed is likely to vary depending upon the skill and experience of the new interviewer. It will be at the discretion of the clinical coordinator to determine the new interviewer's readiness for study participants.
- For self-administered questionnaires, training should include what to look for in reviewing forms, methods of getting clarification from participants, and comfort in administering the forms as interviewer-administered forms when participants don't complete them on their own.
- All training should include a review of legibility and completeness of a new interviewers forms.

10.6 Quality Control Procedures-See Quality Control Document.

Section 10 – Appendix

A. Site Specific Procedures for Responding to the Post–Partum Depression Questions

1. **COLORADO**
2. **FINLAND**
3. **GEORGIA/FLORIDA**
4. **GERMANY**
5. **SWEDEN**
6. **WASHINGTON**

B. Child Behavior Checklist Frequently Asked Questions (FAQs)

C. Model Instructions for Parent for Completion of Child Behavior Checklist

D. Model Letter for Child's Pediatrician/Specialist Conveying Child Behavior Checklist Results (ONLY TO BE SENT AT PARENT'S REQUEST)

E. Site Specific Pubertal Assessment Cover Letters

1. **COLORADO**
2. **FINLAND**
3. **WASHINGTON**

F. Model Letter to Child Explaining Junior Scientist Book #3

G. Site Specific Letter to Child Explaining Junior Scientist Book #3

1. **COLORADO**

H. Script for Explaining Questionnaires (child and parent versions))

I. Site Specific Scripts for Explaining Questionnaires

1. **COLORADO**

J. Questionnaire Cover Sheets (CLE list, First Child Questionnaire, Annual Child Questionnaire)

K. SDQ Explanation Script, Email Notification Script, and Parent Notification and Referral Process

A1: Site Specific Procedures for Responding to the Post–Partum Depression Questions: Colorado

TEDDY Colorado Site: Postpartum Depression Referral and Child Abuse Reporting Procedures

TEDDY Colorado has a staff psychologist available for referrals from the TEDDY Study. Donna Follansbee has extensive experience working with people with Type 1 diabetes and is familiar with the TEDDY Protocol. Her contact information is available in the TEDDY lab. See Appendix 1 for Driving directions that can be given to subject if requested or needed.

Donna Follansbee, Ph.D.
1720 S. Bellaire St.
303-756-2198 (office)
303-851-5913 (pager)
303-843-9514 (home)
303-756-1413 (fax)

Psychological Evaluation Tools

The following tools are used to measure parents' psychological responses to TEDDY (Protocol Section 8.7.4.3) in various TEDDY parental questionnaires.

- Edinburgh Postnatal Depression Scale – Integrated into the 6-month clinic visit questionnaire.
- State-Trait Anxiety Inventory, STAI (6 items) - Integrated into the First Questionnaires and questionnaires administered at 6, 15, and 27-month visits and annual visits thereafter. In addition, these questions are administered at a clinic visit following a family being informed of persistent autoimmunity.
- Depression Scale (6 items) from Bradley's Well-Being Questionnaire – Integrated into the self-administered annual parent questionnaire at 15- and 27-month visits.

Only the Edinburgh Postnatal Depression Scale will be scored and used as a basis for referrals. The other 2 scales are intended as research measures for the TEDDY study. These instruments were not designed for clinical use or for a basis of referrals. In addition to the Edinburgh scale, clinical judgment related to concern for the subjects' psychological health should prevail. This is discussed below.

Edinburgh Postnatal Depression Scale

Parents (Mother required, father too if possible) respond to these questions on the 6 Month Questionnaire, Question 6 which is then reviewed/scored by the clinic staff. It is the Mother's responses that are required to be reviewed/scored and

referral made. Completed father questionnaires should also be reviewed for referral but the collection is not a required part of the protocol.

Refer to psychologist if score is 13 or greater or if the answer to 6j is anything other than never

6. Some parents get the baby blues after the birth of the child. Here are some questions about the baby blues. Please, think about the time since this child was born for each question and then mark an answer.

a. You have been able to laugh and see the funny side of things.

[ ] As much as I always could (0)
[ ] Not quite so much now (1)
[ ] Definitely not so much now (2)
[ ] Not at all (3)

b. You have looked forward with enjoyment to things.

[ ] As much as I always did (0)
[ ] Rather less than I used to (1)
[ ] Definitely less than I used to (2)
[ ] Hardly at all (3)

c. You have blamed yourself unnecessarily when things went wrong.

[ ] Most of the time (3) [ ] Some of the time (2) [ ] Not very often (1) [ ] Never (0)

d. You have been anxious and worried for no good reason.

[ ] Not at all (0) [ ] Hardly ever (1) [ ] Sometimes (2) [ ] Very often (3)

e. You have felt scared or panicky for no good reason.

[ ] Quite a lot (3) [ ] Sometimes (2) [ ] Not much (1) [ ] Not at all (0)

f. Things have been getting on top of you.

[ ] Most of the time you haven't been able to cope at all (3)
[ ] Sometimes you haven't been coping as well as usual (2)
[ ] Most of the time you have coped quite well (1)
[ ] You have been coping as well as ever (0)

g. You have been so unhappy that you have had difficulty sleeping.

[ ] Most of the time (3) [ ] Sometimes (2) [ ] Not very often (1)
[ ] Never (0)

h. You have felt sad and miserable.

[ ] Most of the time (3) [ ] Some of the time (2) [ ] Not very often (1)
[ ] Never (0)

i. You have been so unhappy that you have been crying.

[ ] Most of the time (3) [ ] Quite often (2) [ ] Only occasionally (1)
[ ] Never (0)

j. The thought of harming yourself has occurred to you.

[ ] Quite often (3) [ ] Sometimes (2) [ ] Hardly ever (1) [ ] Never (0)

Assessment of Psychological Distress by Clinical Staff

The clinical staff seeing the TEDDY family may have concerns related to psychological distress that they observe during the course of any clinic visit, independent of the Edinburgh Scale or other research measure responses. Clinical judgment should be used to assess the level of this distress and if the clinical staff thinks that a referral might be warranted, a conversation should occur that offers this option and the referral process described below should be followed.

Referral Process

If a referral is required, the following steps will be taken by TEDDY staff:

- Inform family that the answers to the questions on Page 3 are used to measure baby blues or postpartum depression that Moms sometimes experience after the baby is born and that based upon their responses (to the Edinburgh Scale questionnaire or based on clinical staff concerns), it is important for us to see how we can provide some helpful support. We would like for them to speak with our TEDDY Psychologist so they have the opportunity to discuss how they are feeling with someone who understands postpartum depression. We are seeking permission for the Psychologist to contact them directly or determine if they would rather initiate the contact with her, or are they under the care of a health care provider currently. The following questions should form the basis of the referral:
    - Have you told your doctor or anyone else about your feeling blue or having thoughts of hurting or harming yourself? (YES or NO).
    - Are you currently receiving treatment for these feelings? (YES or NO).

      IF YES or NO: Inform the family we have a Psychologist on staff, Dr. Donna Follansbee who is available to speak with them specifically about the "baby blues" or thought of hurting or harming themselves.

      IF YES: Provide mother Dr. Follansbee's name and contact info on the referral checklist.

      IF NO: We feel it is very important for you to speak with someone regarding this matter. It would be advisable to see your general physician, call or go to the local health department. It may be a good idea for us to contact Dr. Follansbee and have her call you to talk more about your feelings. Would this be OK with you? Should you continue to feel blue or think about harming yourself, please contact either your primary care physician, this referral therapist, or call us at (303) 315-0115. Ask for: Michelle or Tricia.

- A referral Checklist should be filled out. This contains the following 1) elements of the conversation that would be good to include, 2) Dr. Follansbee's contact information (including driving directions) as well as TEDDY Study Nurse Contact information should they want to talk further, 3) a notation section that allows for staff to write in information from the conversation (e.g. that they are on antidepressants, seeking care) and the specific outcome and 4) staff initials/number and date of the conversation. One copy of this will go in the subject chart and one goes to the subject. This referral checklist should occur regardless of whether someone is being seen by another physician for this issue (frequently their PCP) or not. The outcome of this referral conversation could be one of the following
    - The subject gives permission to the study staff to share the results of this scale to Dr. Follansbee and have her contact them to follow-up. If possible, page Dr. Follansbee at 303-851-5913 prior to conducting any other parts of the TEDDY visit (designed to ensure family talks to psychologist while they are in the clinic) and fax the filled out Edinburgh Scale (page 3) to her.
    - The subject gives permission to the study staff to share the results of this scale to Dr. Follansbee, but requests that they not be contacted by her, rather that they will contact her if needed. Dr. Follansbee's number will be on the copy of the checklist that they receive. Dr. Follansbee should be notified that the referral has been made.
- Have the following information available for Dr. Follansbee when she returns the page:
    - Name of Parents and Child
    - Age of Teddy child, and the ages of the TEDDY child's siblings.
    - Level of Risk of Child (antibody history) and how family has responded to outcomes
    - Reason for Referral (family's responses to questionnaire, clinical judgment, and/or they requested contact)
    - Staff's Gut Level Instinct – Based upon previous interaction with family and current interaction with family, communicate with Dr. Follansbee staff impressions
- Dr. Follansbee will then talk to family on telephone and try to schedule an appointment for the family that day. Her office is located at 1720 South Bellaire St.
- If no contact is made that day with Dr. Follansbee, subject should understand that Dr. Follansbee will be trying to contact them (or them her) and that study staff will check in with them as well.

Psychological Assistance Provided to TEDDY Families

- At the appointment, Dr. Follansbee uses the following assessment methods to further assess family's status and needs.

Dr Follansbee's Family Assessment Guidelines (What will happen when she meet with the family)

- Gather general reason for referral in parents' own words
- Explain role of psychologist: that we will be meeting one or two times to try to address concerns and if parent desires to continue and appropriate referral for ongoing therapy will be made
- If concerns are related to parental anxiety or depression, administer Beck Depression Inventory or Burns Anxiety Inventory
- Conduct mini-mental status on all clients (orientation, Mood, Memory and Cognition, Sleep patterns, Speech, Suicidality Risk, Abuse Risk, Trauma History)
- Gather individual history as relates to presenting problem
- Gather family history (family of origin as well as current nuclear family). Special attention in individual and family history to stressful life events, and presence of chronic illnesses, if any.
- Assess presence and strength of support network for family
- Give DSMIV diagnosis if meets criteria; otherwise, give diagnostic impression and summary
- Document referral plan if any, and if not, explain why not.

- TEDDY Psychologist will see families for a maximum of two visits to assess their needs, address issues and identify whether further assistance is necessary. If a family requests additional assistance or TEDDY Psychologist recommends additional assistance, Dr. Follansbee will provide family with appropriate referral options for further treatment.

Reporting Suspected Child Abuse

If clinic staff suspect child abuse (physical or psychological) during a clinic visit, it is required that they report the abuse to the appropriate authority in the county in which the family resides. These phone numbers are available in the TEDDY laboratory.

A new reporting telephone list will be printed each year to ensure we have the most current list of numbers. These numbers are available through the Colorado Department of Human Services Division of Child Welfare Services web site: http://www.cdhs.state.co.us/cyf/Child_Welfare/County_Phone_Numbers.htm

A2: Site Specific Procedures for Responding to the Post–Partum Depression Questions: Finland

1. All TEDDY personnel are specially trained to recognize symptoms of post-partum depression in the parents of the TEDDY child.

2. Personal discussions and support are offered at every contact with TEDDY study personnel.

3. Study nurses evaluate the coping of the families, and readily refer them to the TEDDY doctor if any indications of emotional distress/depression are present.

4. If specific supporting measures are needed, the families are referred to the local psychiatric teams.

A3: Site Specific Procedures for Responding to the Post–Partum Depression Questions: Georgia/Florida

1. Any TEDDY relative (mother, father, or primary caretaker) who completes a depression questionnaire and scores 13 or higher or answers anything but "never" for 7J is identified by the TEDDY staff member reviewing/completing the 6 month questionnaire

2. The TEDDY staff member relays the information to the local TEDDY clinical director (Dr. Schatz or Dr. Muir). The local coordinator and the clinical director decide who will place the call to the family member in question.

3. The TEDDY staff member placing the call talks to the family member, asking if they have discussed the issue with their PCP. If not, we recommend that they do. If they have no PCP, we offer to help them find a local resource through the community mental health program. If the family refuses to talk to anyone about their responses, we note the information on the physical exam form in the referral section. Adverse event reports are submitted for all.

A4: Site Specific Procedures for Responding to the Post–Partum Depression Questions: Germany

If the depressive mood continues longer than 4-8 weeks after the TEDDY visit, the Diabetes Research Center provides the mother with documents about counselling centers, psychologists and psychiatrists in the area where the family lives. If the mother or the family have any questions regarding the materials they can contact the TEDDY center.

The procedure:

Mothers who score higher than 13 on the Edinburgh Postnatal Depression Scale are contacted by phone. They are asked about questions that they received scores equal to or higher than a score of 2. Sometimes the problems seem to be temporary and they simply need more time to cope. They are called again after 4-8 weeks and asked whether the problems are still there – if yes, they get a letter with addresses of counselling centers, psychologists or psychiatrists in the area they live.

A5: Site Specific Procedures for Responding to the Post–Partum Depression Questions: Sweden

TEDDY Sweden has no access to mental health staff within the clinics of the hospital. Therefore parents who need psychotherapy or counseling - according to the scores on PPD-scale – need to approach psychologists, psychotherapists or psychiatrists who have private clinics. Generally it is very hard to get access to these persons – especially within a short notice – and usually it is also quite expensive. Depending on the need of the parents TEDDY Sweden is building up a network of a few psychotherapists in the Region who will agree to see these parents with relative short notice. TEDDY will also pay for five sessions to facilitate for the parents to use this possibility.

As TEDDY recruits children from quite a large area and has three clinics, it has been hard to predict how many parents would ask for this help, and where they would live. Therefore we have waited to do more extensive contracting of psychotherapists until we have more data about what will be required.

It should be noted that the child health care centers, where all parents take their children for check ups, vaccinations etc have access to mental health staff who are available for counseling. Also, in some centers they administer the same PPD-scale to the mothers and should have a plan for referrals.

Our experience after more than two years is that most parents who score high on the PPD-scale, already have someone that they can talk to or is getting treatment/counseling somewhere. Up until now two mothers have been referred to a psychotherapists. With this low number of parents needing referrals, we will continue to solve the need of each parent on an individual basis within the informal network.

The Instruction for the nurses is the following:
If a parent on the 6 Month Questionnaire answers something else than “never” on question # 7j or the total sum of the scores of the parent’s answers is 13 or more, it is an indication that the parent might be depressed.
The nurse will note this and say the following:

Have you talked to someone else that you are depressed (or have had thoughts of hurting yourself)?
Do you get any treatment for this or have someone you can talk to about?
If NO *Would you like that we help you find someone to talk to about your thoughts and feelings?*
If YES *We have some psychotherapists who have agreed to be available to TEDDY parents. Should I ask one of these persons to contact you? If you want TEDDY can pay for 5 sessions with this psychotherapist.*
If NO *Even if you don’t want to have our help to contact anyone, it is important that you yourself find someone that you can talk with. Have you an idea about who you could contact? Do you want me to call you within a couple of weeks and check with you how things are going?*

If the parent wants to see a psychotherapist or counselor the nurse will get in touch with the study coordinator who will arrange the referral to a therapist.

A6: Site Specific Procedures for Responding to the Post–Partum Depression Questions: Washington

Referral Process

If a parent scores over 13 on the PPD scale or responds anything but NEVER for 7J, referral is required and TEDDY staff will take the following steps:

- The clinic staff member who conducted the interview will notify the clinic coordinator of the parent's score.
- The clinical coordinator will then notify a senior coordinator with clinical and/or psychological experience.
- The senior coordinator will determine, based on the responses, to directly contact the individual or to have the PI make the contact. The assigned contact will call and inform the family of the support services available to them.
    - The family will be contacted about their responses to some of the questions during the interview.
    - The staff member will ascertain the current status of the individual and whether or not they are currently receiving care for depression/anxiety.
- If the individual is not currently under care the TEDDY staff will offer a referral to a health care provider (i.e. Psychologist, therapist, counselor). Therapists have been selected on their expertise in this area, geographic location and ability to see families with differing income levels.
    - Whether or not to contact the therapist is left to the family to initiate unless otherwise requested by the family.

B. Child Behavior Checklist Frequently Asked Questions (FAQs)

1. **What is the Child Behavior Checklist?**
   The Child Behavior Checklist (CBCL) is a measure of child behavior from the parent's point of view. It tells us about many kinds of common child behaviors. It tells us about behaviors like activity level. It tells us about the child's attention span. It tells us whether the child is easy or difficult to manage. It tells us about a child's feelings. It tells us whether the child might be unhappy or worried. It also tells us something about how the child is developing. The Child Behavior Checklist cannot diagnose your child with a problem. But, it can tell us if your child's behaviors are similar to the behaviors of other children the same age.

2. **What if my child scores high on the Child Behavior Checklist?**
   A high score on the Child Behavior Checklist does not mean your child definitely has a behavior problem. But we think taking your child to a behavior specialist could be helpful. The specialist can carry out a more complete evaluation. The specialist can tell if your child has a behavior problem. The specialist can help you understand what kind of problem the child has. The specialist can also help you manage the child's problem better. If you do not know who to take your child to, we will help you find someone.

3. **Why are we using it in TEDDY?**
   The Child Behavior Checklist is a form filled out by parents all over the world. It tells us about a child's behavior. We can use the Checklist to see if children who get diabetes have different behaviors than children who do not get diabetes.

4. **Could filling out the Child Behavior Checklist help my child?**
   The Child Behavior Checklist could find a behavior problem early. If child behavior problems are found early, they are much easier to treat.

5. **What if both parents want to fill out the Child Behavior Checklist?**
   If both parents want to fill out the Checklist, ask them to fill it out together.

6. **Will my child's Child Behavior Checklist results be confidential?**
   Yes. We will not show your answers to the Child Behavior Checklist to anyone outside of the TEDDY study.

7. **Will you share my child's results with my pediatrician or anyone else?**
   No. But if you want us to share the results with someone, you have to tell us in writing.

8. **What should I do if my child gets a high score on the Child Behavior Checklist?**
   We think you should take your child to behavior specialist. The specialist can do a more complete evaluation. The specialist can tell whether your child has a

behavior problem. If so, the specialist will help you understand what the problem is and what you can do about it.

9. **Some of the questions on the Child Behavior Checklist seem to be asking the same thing? Do I have to fill in all the items?**
   Yes. Please fill in all of the items. If two items seem to be asking the same thing, answer them in the same way.

10. **I filled out the Child Behavior Checklist last year. Why do I need to do this again this year?**
    Children's behaviors change over time. For some children, there are big changes in behavior from one year to the next. For other children, there are only small changes. When you fill out the Child Behavior Checklist each year, you tell us how your child is changing.

11. **I am worried about my other (non-TEDDY) child. Can I fill this out for my other children too and have it scored?**
    The TEDDY study has money to give the Child Behavior Checklist for the TEDDY child only. If you are worried about another child, we think you should take that child to a behavior specialist. We will give you names of specialists who may be able to help.

    Grade 6.0

C. Model Instructions for Parent for Completion of Child Behavior Checklist

Dear _____ (fill in child's primary caretaker),

The Child Behavior Checklist is a form filled out by parents all over the world. It tells us about a child's behavior. We can use the Checklist to see if children who get diabetes have different behaviors than children who do not get diabetes.

Please fill in this form about your TEDDY child. We want your ideas about the child even if other people might not agree. Tell us about your child's behavior in the last two months.

If both parents want to fill in the form together, that is ok.

Be sure to answer all items. If you have a question, call us at _____.

Please bring this to your next TEDDY visit. Or send it back to us in the stamped envelop we have given you.

Thanks for your help!

(grade 4.5)

D. Model Letter for Child's Pediatrician/Specialist Conveying Child Behavior Checklist Results (ONLY TO BE SENT AT PARENT'S REQUEST)

Dear _____ (pediatrician or other child specialist),

_____ (child's name) is currently participating in a study at our institution. As part of the study, we give the Child Behavior Checklist when the child is 3-5 years old. As you may know, the Child Behavior Checklist is a form filled out by parents all over the world. It tells us about common child behaviors. Because it is used world wide, we are able to compare a child's score to other children of the same sex and age. The Child Behavior Checklist is often used to screen children for behavior problems. It cannot diagnose a problem. However, we think that a child with a high score should see a child specialist for further evaluation.

We are writing to you because _____ (child's parent) has asked us to share the results of the Child Behavior Checklist with you. _____ (child's name) received a high score on this measure. The high score suggests …….. (fill in depending on the child's score as indicated below)

I. High Externalizing Behaviors: the child may be more active or difficult to manage than other children the same age.

A. High Attention Deficit/Hyperactivity Behaviors: the child may be more active of have greater difficulty paying attention than other children the same age.

B. High Oppositional Defiant Behaviors: the child may be more difficult to manage than other children the same age.

II. High Internalizing Behaviors: the child may be unhappy or more worried compared to other children the same age.

A. High Affective Behaviors: the child may be unhappy compared to other children the same age.

High Anxiety Behaviors: the child may be shy or worried compared to other children the same age.

III. High Pervasive Developmental Problems: the child may be developing more slowly than other children the same age.

We believe that the child's high score warrants further evaluation. If a behavior problem is confirmed, early treatment is often quite successful. Thank you for your assistance in this matter. Please contact us if you need additional information.

Sincerely,

E.1A: Site Specific Pubertal Assessment Cover Letters: Colorado (English)

COMIRB
APPROVED
26-Jul-2013

The Environmental Determinants of Diabetes in the Young

Dear TEDDY Parent,

TEDDY would like to collect information on how your child progresses through puberty. Most children start to go through puberty between 8 and 12 years of age. The reason for collecting this information is to learn more about how puberty may affect diabetes risk.

The Pubertal Assessment form allows you and your child to choose a picture of what they look like at this time. We encourage you and your child to complete this form together. It is okay for you to complete the assessment for your child, however we think your child should know that you are providing this information to TEDDY.

This information is important to the study. Please remember that your participation in TEDDY is voluntary. If you or your child chooses to decline this part of the study, it will not change your participation in the rest of the TEDDY Study. If at any time you change your mind, you can stop completing this form.

Thank you for your participation.

TEDDY Colorado

Parent Letter for Pubertal Assessment 7172013

E.1A: Site Specific Pubertal Assessment Cover Letters: Colorado (Spanish)

Estimado padre de TEDDY,

Al estudio TEDDY, le gustaría recolectar información acerca de cómo se desarrolla su hijo/a durante la pubertad. La mayoría de los niños entran a la pubertad entre las edades de 8 y 12 años de edad. La razón por la cual se está recolectando esta información es para saber más acerca del posible efecto que pueda tener la pubertad en los riesgos de la diabetes.

El formulario de Evaluación Puberal le permite a usted y a su hijo/a elegir una imagen con la cual él o ella se identifiquen en esta etapa de su desarrollo. Recomendamos que usted y su hijo/a completen este formulario juntos. Usted puede completar el formulario para su hijo, pero consideramos que sería bueno que su hijo/a sepa que usted esta proveyendo esta informacion al estudio TEDDY.

Esta información es importante para el estudio. Porfavor, recuerde que su participación en el estudio TEDDY es completamente voluntaria. Si usted o su hijo/a deciden no tomar parte en esta porción del estudio, no cambiara el resto de su participación en el estudio TEDDY. Si en cualquier momento usted decide cambiar de opinión, usted puede dejar de completar este formulario.

Gracias por su participación

TEDDY Colorado

NIVEL ESCOLAR: 7.2

E.2: Site Specific Pubertal Assessment Cover Letters: Finland

PUBERTY SCRIPT: TO BE USED BY TEDDY STAFF TO EXPLAIN USE OF PUBERTY FORMS EITHER IN PERSON WITH THE PARENT AND CHILD OR AS A LETTER SENT AHEAD OF TIME TO PARENT TO EXPLAIN FORM.

Päiväys:

Hyvät TEDDY-lapsen vanhemmat,

Useimmilla lapsilla puberteetti eli murrosikä alkaa kahdeksan ja kolmentoista ikävuoden välillä. Murrosiän hormonimuutokset vaikuttavat myös voimakkaasti sokeriaineenvaihduntaan. Murrosiässä insuliinin vaikutus heikkenee, jonka takia tarvitaan entistä enemmän insuliinia normaalin verensokeritason säilyttämiseksi. Tämä vaikuttaa sokerirasitustuloksiin ja mahdollisesti alttiuteen sairastua tyypin 1 diabetekseen. TEDDY-tutkimuksessa halutaan ottaa murrosiän muutokset huomioon tuloksia analysoitaessa. Jotta tämä voitaisiin tehdä, TEDDY-tutkimus kerää tietoa lapsenne murrosiän kehityksestä kyselylomakkeen ja lapsen oman arvioinnin perusteella. Tiedon keräämisen tavoitteena on siis ymmärtää paremmin, kuinka murrosikä vaikuttaa tyypin 1 diabeteksen kehittymisen riskiin.

Lapsenne voi joko yksin tai teidän kanssanne valita oheisesta lomakkeesta sen kuvan, joka vastaa hänen tämänhetkistä murrosiän kehitystään. Tämä tieto on tutkimukselle erittäin tärkeää ja arvostamme osallistumistanne.

Kiittäen,

TEDDY-tutkijat

E.3: Site Specific Pubertal Assessment Cover Letters: Washington

Dear TEDDY child and parent,

Puberty begins between the ages of 8 and 12. This is also a time when diabetes sometimes first appears.

During puberty, hormone levels change. This causes rapid changes in the body. As part of the TEDDY study, we want to know if the change in hormone levels during puberty affects getting type 1 diabetes.

We can estimate the level of hormones in TEDDY children by looking at the physical changes in their body.

Together please take a look at the pictures that represent different stages of body changes. The TEDDY child and parent should choose the picture that best shows how your child looks at this time. Or the TEDDY child can choose to complete the form on his/her own, if that feels better. The picture chosen will give us clues about hormone levels.

Your responses are important. They will help us better understand the link between puberty and diabetes.

All information you give to TEDDY is kept private. If you have any questions or concerns please feel free to contact us.

Thank you for all your help with the TEDDY Study.

Sincerely,

TEDDY Team

Reading Level 6.5

F. Model Letter to Child Explaining Junior Scientist Book #3

Hi TEDDY Junior Scientist,

You are growing up so fast! You are now old enough to learn a bit more about TEDDY and why you participate in TEDDY. The book *Will and Emma: Meet the TEDDY Scientists* is included to help you understand why you are in TEDDY.

The book explains TEDDY and diabetes while you can read about Will and Emma on a fun and exciting adventure through the body on the TEDDY Explorer!

The book will also help prepare you for your first TEDDY questionnaire. At the next visit we will ask you to fill out your own TEDDY questionnaire!
Please share this letter with your parents. We would like you to read the book before you come to your 10-year TEDDY visit.

We hope you enjoy it! See you aboard the TEDDY Explorer!

Sincerely,
TEDDY

G1. Letter to Child Explaining Junior Scientist Book #3 – Colorado

Hi TEDDY Junior Scientist,

You are growing up so fast! You are now old enough to learn a bit more about TEDDY and why you participate in TEDDY. The book *Will and Emma: Meet the TEDDY Scientists* is included to help you learn about diabetes and understand why you are in TEDDY.

In this book you will read about Will and Emma going on a fun and exciting adventure through the body on the TEDDY Explorer!

The book will help prepare you for your next visit when we will ask you to fill out your own TEDDY questionnaire!

Please share this letter with your parents. We would like you to read the book before you come to your 10-year TEDDY visit.

We hope you enjoy it! See you aboard the TEDDY Explorer!

Sincerely,
TEDDY

H. Scripts for Explaining Questionnaires (child and parent versions)

Parent Focused Script for Questionnaire Introduction:
"Now that your child is almost 10 years old, we want to ask him/her directly about his/her thoughts and feelings related to TEDDY. There are a number of reasons we think this is important. First, we think it is important to let your child know that we value what they think and feel. This helps him/her to feel more of a part of TEDDY. Second, it can help us better understand how your child feels about being in TEDDY, how they understand TEDDY, and how certain things may impact their risk of getting diabetes. By the age of 10, children are usually very good at telling us about their thoughts, feelings, and behaviors. By getting information from your child, along with information from you, we can get the most complete data from your family to help us figure out what impacts the development of diabetes.

When your child completes the questions, it's important that they know there are no right or wrong answers. It will also be important for your child to complete the questionnaires on his/her own, without your help. Sometimes, children give different answers when adults help. If your child has trouble reading a question, we can read it to them, so you won't have to. If they still have trouble understanding the question, that's okay, they can just skip that question. Since we will be giving the same questions to kids up to the age of 15, there's a good chance that younger kids may have trouble understanding a few of the questions. We really appreciate you being willing to let your child answer these questions – this is such an important part of TEDDY!"

Child Focused Script for Questionnaire Introduction:
"Now that you're almost 10 years old, we want to hear what you think and feel about TEDDY! We've been having your parents answer questions since you were a little baby, but now it's your turn to answer questions, too. This will really help us understand what you think and feel about TEDDY and know what important things have happened to you since your last visit to TEDDY.

When you answer the questions, remember that there are no right or wrong answers. We just want to know what you think and feel. It's important that you do these questions all on your own. Some of the questions have big words. Lots of kids need help reading some questions, so if you need help, just let me know and I can read a question out loud for you. If you still aren't sure about what a question means, that's okay. Just skip that question. We're so happy that you're old enough to do questions all on your own now!!"

Notes about the use of these scripts:
These scripts provide examples for language you can use with families. Please feel free to shorten or edit scripts to better fit with your site's procedures. These scripts are intended to be used when questionnaires are first discussed with the family. However, some of the information (e.g., second paragraph focusing on questionnaire administration) should be repeated at the 10-year visit when the child first completes the questionnaires.

I. Site Specific Scripts for Explaining Questionnaires – Colorado

Dear TEDDY Parent,

Now that your child is 10 years old, TEDDY would like to collect information on what he/she thinks and feels about participating in TEDDY. The reason for collecting this information is to learn more about how children's experiences and feelings affect diabetes risk. We also want to understand how your child feels about being in the TEDDY study.

Your child's thoughts and feelings are very important to us. While we will encourage you to look over the questionnaire, we would like for the TEDDY children to complete the questionnaire on their own. There are no right or wrong answers and your child can ask staff for help or skip questions that are not understood.

Remember the *Will & Emma: Junior Scientists* book we gave you at 6 ½ years? Now we have another story about Will & Emma that will be mailed to your child shortly before the 10 year visit. This book will give your child information about TEDDY and will get her ready for telling us about her thoughts and feelings. (optional short description of book)

The information the TEDDY children share is important to the study. Please remember that you and your child's participation in TEDDY is voluntary. If you or your child chooses to decline this part of the study, it will not change your participation in the rest of the TEDDY Study. If at any time you, or your child, change your mind in the future, your child can stop completing this questionnaire.

Thank you for your participation.

TEDDY Colorado

J. Questionnaire Cover Sheets (CLE list, First Child Questionnaire, Annual Child Questionnaire)

Child Life Events List: *We want to know about things that may have happened since your last visit to TEDDY. Some kids have a lot of these things happen, some kids have just a few, and some kids have none of these things happen. There are no right or wrong answers. Remember, it is up to you if you want to do these questions or not. Your answers are important to us, but we will keep them private.*

Please read the list of things on the next pages by yourself. If you have trouble reading one, let us know. Circle things (or tell us out loud) that have happened to you since your last TEDDY visit. Then we will ask you a few more questions about how good or bad these things were.

Child First Questionnaire: *We want to know how you feel and think about being in TEDDY. There are no right or wrong answers. We won't tell anyone your answers. Please do the questions on your own, but let us know if you need help reading some of them. You can also skip ones that you don't understand. It is up to you if you want to do these questions or not. Thank you so much for helping us learn more about what you think and feel!*

Child Annual Questionnaire: *It's that time when we ask how you feel about being in TEDDY. We know that your feelings may change as you get older, so that is why we ask these questions every year. Please remember that there are no right or wrong answers. We won't tell anyone your answers. Please do these questions on your own, but let us know if you need help reading some of the questions. You can also skip ones that you don't understand. Remember, it is up to you if you want to do these questions or not. Thank you so much for helping us learn more about what you think and feel!*

K. SDQ Explanation Script, Email Notification Script, and Parent Notification and Referral Process

SDQ Explanation Script

We want to know more about how your child thinks, feels, and behaves outside of TEDDY. When you answer these questions, think about your child's behavior over the last 6 months. Please remember that there are no right or wrong answers. It is up to you if you want to do these questions or not. Thank you so much for helping us learn more about your child!

SDQ email notification text for sites

The following text will be included in the email to staff when a child's scores were elevated on one or more domains:

Script if the child is elevated on Internalizing:

"We received the results from the Strengths and Difficulties questionnaire that you and your child completed. Responses from your family indicated that your child's score on questions related to emotions and/or problems with social interactions was high compared to other children his/her age. This suggests your child may be struggling in these areas but does not definitely mean your child has a problem. We recommend that you and your child discuss these difficulties with a doctor or mental health professional to see if your child would benefit from help. We can provide you with contact information for professionals you can speak to about this, if you do not already have this resource."

Script if the Externalizing is elevated:

"We received the results from the Strengths and Difficulties questionnaire that you and your child completed. Responses from your family indicated that your child's score on questions related to behavior and/or attention problems was high compared to other children his/her age. This suggests your child may be struggling in these areas but does not definitely mean your child has a problem. We recommend that you and your child discuss these difficulties with a doctor or mental health professional to see if your child would benefit from help. We can provide you with contact information for professionals you can speak to about this, if you do not already have this resource."

Script if both Internalizing and Externalizing are elevated:

"We received the results from the Strengths and Difficulties questionnaire that you and your child completed. Responses from your family indicated that your child's score on questions related to emotions and/or problems with social interactions and your child's score related to behavior and/or attention problems was high compared to other children his/her age. This suggests your child may be struggling in these areas but does not definitely mean your child has a problem. We recommend that you and your child discuss these difficulties with a doctor or mental health professional to see if your child

would benefit from help. We can provide you with contact information for professionals you can speak to about this, if you do not already have this resource."

Parent Notification and Referral Process

Each site will develop a standardized process for notifying TEDDY parents when their child's score is elevated on one or more of the SDQ domains. Sites do not need to notify families when their child's score is not elevated (i.e., normal). While there will be small differences each site's notification process, all processes will include the following elements:

1. *Timely notification*. Sites will preferablely attempt to contact parents by phone or mail within one week of their study visit to inform them of SDQ elevations.
2. *Provision of information about the type of elevation*. Sites will utilize the email notification script to provide parents with the type of elevation their child has (i.e., Internalizing and/or Externalizing).
3. *Provision of referral resources*. Each site will provide parents whose child has an elevated score with one or more resources for obtaining further psychological/behavioral evaluation. These resources may including referring parents to community mental health centers, specific local mental health practitioners, school counselors, nurse case managers, and/or pediatricians. Each site has identified resources available in their area. If sites speak with parents by phone, a follow-up document should be provided via mail (preferred) or at the next study visit that provides a printed list of the referral resources.

Challenges with the parent notification process should be immediately reported to the Psychosocial Committee for discussion and guidance.

11.0 TEDDY Book

At the 3 month clinic visit, the primary caretaker (usually the mother) will be introduced to the TEDDY Book. This is a notebook that is to be used by the primary caretaker to record events in their child's life that are of interest to the study. Primary caretakers are instructed to write down things such as when new foods are introduced to the child's diet, use of dietary supplements, medications, vaccinations, length and weight history of the child, illnesses and symptoms of the child, doctor's visits and hospitalizations, social and daycare interactions, and life events of the child. The primary caretaker will be asked to bring in the TEDDY book to each clinic visit. (See below for detailed instructions.)

At each visit study personnel will go over the TEDDY book with the primary caretaker and extract pertinent information using standardized study forms. It is not mandatory for the child's primary caretaker to use the TEDDY book, but the primary caretaker should be encouraged to use the book to record what happens to the child between clinic visits. The aim of the book is to make it easier for the primary caretaker to recall what has happened to the child between the clinic visits and to help improve efficiency of each study visit. The TEDDY book might also serve as a contact- and rapport-building tool between parents and TEDDY personnel.

The first TEDDY book the parents receive will be used up until the age of two years. The second TEDDY book the parents receive will be used from 2-5 years of age. Both books are discussed in this MOO section.

The parents will receive the TEDDY calendar to be used from 6-9 years of age. Detailed instructions for use of the TEDDY calendar are discussed in MOO section 11.4.

11.1 Introduction of the TEDDY Book

At the first study visit show the book to the mother (parents or primary caretaker) and fill in the child's name.
Explain the purpose and use of the TEDDY book including:

- The aim of the book is to help the parent remember what happens to the child between study visits,
- The TEDDY book works best if it is filled in frequently – for example once a week or every second week,
- Filling in the TEDDY book will make the study visits shorter, and
- Parents will be allowed to keep the first book after the child has reached two years of age and will be allowed to keep the second book after the child has reached five years of age.

Complete page two with names, addresses, telephone numbers etc. together with the mother (father, parents or primary caretaker). (For simplicity reason "mother" will be used as the person coming with the child to the first visit even though this person can be the father, both parents, or another primary caretaker)

11.2 Instructions on how to fill in the TEDDY Book

Study staff should turn the pages of the book one at a time and explain the purpose of each page to the mother. Specify how each page should be filled in (if applicable). On each page, record events that have already taken place (e.g., the baby's early diet).

Table of Contents: Lists the content of the book.

Information about TEDDY: This section provides a short summary of the study and describes what will happen – what to expect - at the study visits. Study staff should also stress that parents are always welcome to call if questions arise about the study, pointing out the staff contact information provided in the book.

Child's Picture Page: This section provides a place to paste the child's pictures as the child grows over the course of the study. The design of the page will be site specific.

Child's Early Diet-Breast Milk and Formula: This section is where breast-feeding and introduction of all formulas should be recorded. Help the mother fill in what the child has been fed until today. The TEDDY Book for 2-5 year olds only contains the section on breast-feeding; the formula section is not included in this book.

Introduction of New Food Items: This section is only in the TEDDY Book used for birth-2 years; the TEDDY Book for 2-5 year olds does not contain this section on Introduction of New Food Items. This section should be filled in when the child is given something other than breast milk or formula. The list should only be filled in when the child gets something the first time. Even small, tiny tasting portions should be recorded. If the mother is uncertain where to record a special item, the last rows can be used. The interviewer should, however, always when possible transfer the foods from "other" category to specific categories. Show the mother the grouping of the food items: a) Fruit and berries; b) vegetables; c) corn and grains; d) meats and meat products; f) dairy products. If applicable, help the mother fill in all food introduced up until today. If the child was given jar or box baby food or cereal, or other food, try to obtain the specific name brand and type of food. Sometimes, parents are not aware of the specific food ingredients, so obtaining the brand name will be helpful, and it will also be helpful with the 24-hour food recall that takes place during the 3-month interview. Visual aids of brand name products are found in TEDDY clinics, and showing these visual aids may help clarify the caretaker's memory of a specific food.

Other Diet Choices: This section is in the TEDDY Book for birth-2 years; it is given a new title of All Special Diets and placed after the Allergies section in the TEDDY Book for 2-5 year olds. This section needs to be filled in if the child is given a special diet because of allergy to cow's milk, cereal or wheat (other avoidance diets due to allergy do not need to be indicated), celiac disease, cultural beliefs or other reasons.

Allergies: In both the TEDDY Book birth-2 year and TEDDY Book 2-5 year all allergies should be recorded in the Allergies section, regardless of whether they have been indicated in the All Special Diets section or not (for example if a subject is avoiding cow's milk due to an allergy, this is indicated in the Other Diet Choices section (for the TEDDY Book birth-2 years) or the All Special Diets section (for the

TEDDY Book 2-5 years) and it should also be indicated in the Allergies section of that TEDDY Book).

Recording of the Child's Weight and Length/height: This section is in both versions of the TEDDY Book. Ask the mother to record all measurements done by a health care provider. The mother can also bring in the child's health care record at each visit. (The measurement done at the visit should be recorded on the Physical Exam Form and not in the TEDDY book.)

Vaccination Record: This section is in both versions of the TEDDY Book. Ask the mother to record the dates when the child has been given vaccinations. Have her record all vaccinations given to date. At future study visits, the mother can also bring in the child's health care record; when the parent brings in the vaccination card to the TEDDY visit the site should make a copy of the card for the child's TEDDY records.

Vitamins, Multivitamins, Minerals, and other Dietary Supplements: This section is in both versions of the TEDDY Book. In this section, caretakers should record all vitamins, multivitamins, minerals and other dietary supplements given to the child, including dietary supplements taken for a medical condition/illness (this includes products such as Tums and Rolaids whose active ingredients consist only of vitamins, minerals and/or other dietary supplements), except those listed below and those supplements listed in the "Do Not Code" section of the "Diet TEDDY Coding Decisions" document which can be found under the Diet Committee section of the TEDDY website:

- Do not code any products that are purely homeopathic in the dietary supplements section. Sites should review the complete ingredient list of the product before classifying it as purely homeopathic. If the product contains added vitamins, minerals probiotics, etc then it should be coded in the dietary supplements section. If the product is deemed to be purely homeopathic, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken for a medical condition then it should be coded under the medications section. A homeopathic product can be identified by label. Doses for homeopathic products have the Roman numeral listed in the recommended doses, with a C, M, or X, such as 6X, 12C, 5M, etc. In Europe and some other parts of the world you will see the letter D or DH. This refers to decimal or 1/10 which is the same as X, used in the U.S. Also in Europe the position of the number and letter designation are reversed from the US designation. So you will see such designations as D5 or D10 which are equivalent to 5X and 10X. You will also encounter CH and CK, these are equivalent to C, referring to the Centesimal or 1/100 dilution rate.
- Do not code any products that are purely herbal in the dietary supplements section. Sites should review the complete ingredient list of the product before classifying it as purely herbal. If the product contains added vitamins, minerals, probiotics, etc then it should be coded in the dietary supplements section. If the product is deemed to be purely herbal, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken for a medical condition then it should be coded under the medications section.

Help the caretaker record any preparation that has been given to date.

If the child has been breast fed, try to determine whether "human milk fortifier" or other breast milk supplement was used. Encourage the mother to bring the bottles or containers of the preparation to each and every study visit to help with the identification of the preparation. Use the visual aids showing bottles and boxes of common supplements to help the caretaker identify a particular product. There may be questions about dietary supplements, since so many brands and types of products exist. Please, write the name and type of the dietary supplement as accurately as possible. Of some preparations there are several strengths available and the name can only differ in numbers, e.g., Ascorbin500 and Ascorbin1000. There is a lengthy list of codes to select from for the different brands, but codes cannot cover every brand. If you have a question about coding for a dietary supplement, consult the TEDDY nutritionist at the clinic to help resolve the item. As necessary, the DCC will work with the nutritionists to add codes to cover products as they enter the study population.

Illnesses: This section is in both versions of the TEDDY Book. Tell the mother that it is important for her to record dates the child has been ill as well as the child's symptoms. Go over the list of symptoms sick children can have. For each illness, she should indicate the date of the illness, the symptoms, whether the child had a fever (please note that TEDDY defines a fever as a temperature equal to or higher than 38°C or 101°F), if the child did have a fever whether it was measured or not, the diagnosis (if applicable) and whether or not the illness was diagnosed by the parent or health care provider. On February 6, 2015 the following probe was added to the TEDDY Book data extraction form "*This could be an illness with a fever, any infection, a virus, or other common childhood conditions like pinworms or lice."*

Record any illnesses and symptoms the child has had to date - <u>symptoms should always be recorded, however there may not always be a diagnosis, so diagnosis may be left blank sometimes. For rare situations in which there are no symptoms, a radio button is available on the extraction form to indicate this.</u>

> **<u>Note</u>**: For data analyses completed on fevers (a temperature equal to or higher than 38°C or 101°F) the answer indicated in the column entitled "Fever? (temperature is equal to or higher than 38°C or 101°F)" will be used. Therefore it is important for the site to be sure to always provide an answer for this question on the data extraction form when an illness is indicated.
>
> > After discussion amongst the Coordinators it has been discovered that sites are indicating fevers differently on the TEDDY Book extraction forms (listed below is how each site is recording this data). It has been decided that as long as an answer is indicated in the column entitled "Fever? (temperature is equal to or higher than 38°C or 101°F)" the data entry methods listed below are both acceptable.
> >
> > <u>Indicate answer to "Fever? (temperature is equal to or higher than 38°C or 101°F)" AND indicate fever as a symptom</u>:
> > Sweden
> > Finland

Indicate answer to "Fever? (temperature is equal to or higher than 38°C or 101°F)", but DO NOT indicate fever as a symptom (if no other symptoms they indicate "No symptoms"):
Colorado
Georgia/Florida
Washington
Germany

Note: If an illness diagnosis is made, whether it is made by the parent or the health care provider, the diagnosis code should always be indicated in the illness question. If diagnosed by the health care provider then this option should be marked, if diagnosed by the parent then this option should be marked. If either 'diagnosed by parent' or 'diagnosed by health care provider' is marked a diagnosis code must be indicated. If there is no diagnosis then neither 'diagnosed by parent' nor 'diagnosed by health care provider' should be indicated.

Note: In the Diagnosis column of the Illness question two answer choice options are provided: one for "Diagnosed by parent" and one for "Diagnosed by health care provider". If the healthcare provider does not physically see the child to make the diagnosis (for example the diagnosis is made by the parent describing the symptoms over the phone to the health care provider's office) then the choice "Diagnosed by parent" should be chosen. The choice "Diagnosed by health care provider" should only be selected when the health care provider physically sees the child.

Note: When specific symptoms result in multiple diagnoses each diagnosis and all associated data (illness date, symptom(s) and fever information) should be indicated on a separate data row on the extraction form.

A section to record data on chronic illnesses is available on both versions of the TEDDY Book extraction forms; there is not a separate section for chronic illnesses in the TEDDY Book for the parents. The reason that a separate section has not been provided in the TEDDY Book for parents to record chronic illnesses is because it may be confusing to some parents on how to differentiate between acute and chronic illnesses, therefore it has been decided that the TEDDY staff member should probe the parent for this information and record the illness in the correct section of the TEDDY Book extraction form. A chronic illness has been defined for TEDDY as: "A condition generally lasting 3 months or longer. It is permanent, long lasting or results in residual disability. A chronic disease can also be recurrent and relapse repeatedly with periods of remission". Examples of chronic illnesses of varying severity include: Asthma, Eczema, Rheumatological diseases, Cancer, Hematological conditions (such as bleeding disorders, chronic ITP etc), Epilepsy, Endocrine disorders (such as Diabetes, Autoimmune Thyroiditis, Addisson's Disease, GH-deficiency), Neurological conditions (such as Cerebral Palsy, Multiple sclerosis, varying chronic progressive neurological conditions), Gastroenterological conditions (such as Celiac Disease, Inflammatory Bowel Disease, Crohn's Disease), Congenital heart defects, Malformations, Metabolic disorders.

Medications: This section is in both versions of the TEDDY Book. Medication given to the child should be recorded here**.** All types (oral, topical, injection, etc) of prescription medicine and only oral medications bought "over the counter" are recorded. The mother should record the name of the medications the child has been given to date, together with the reason the medication was given, the child's age when the medication was given and how many days the child received the medication. If the same medication is given on different occasions, each episode should be listed.

If a vitamin, mineral, or other dietary supplement has been recommended or prescribed by a health care provider, the parent may identify it as a medication, but dietary supplements given for a medical condition/illness should not be recorded in the medications section; they should be recorded in the dietary supplements section of the extraction form. The clinic staff should be sure not to list vitamins, minerals and dietary supplements here, but rather list them on the (previous) page for dietary supplements.

> **Note**: The Diet Committee is not interested in pure homeopathic products. Sites should review the complete ingredient list of the product before classifying it as purely homeopathic. If the product contains added vitamins, minerals probiotics, etc then it should be coded in the dietary supplements section. If the product is deemed to be purely homeopathic, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken for a medical condition then it should be coded under the medications section. A homeopathic product can be identified by label. Doses for homeopathic products have the Roman numeral listed in the recommended doses, with a C, M, or X, such as 6X, 12C, 5M, etc. In Europe and some other parts of the world you will see the letter D or DH. This refers to decimal or 1/10 which is the same as X, used in the U.S. Also in Europe the position of the number and letter designation are reversed from the US designation. So you will see such designations as D5 or D10 which are equivalent to 5X and 10X. You will also encounter CH and CK, these are equivalent to C, referring to the Centesimal or 1/100 dilution rate.
>
> The Diet Committee is not interested in pure herbal products. Sites should review the complete ingredient list of the product before classifying it as purely herbal. If the product contains added vitamins, minerals, probiotics, etc then it should be coded in the dietary supplements section. If the product is deemed to be purely herbal, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken for a medical condition then it should be coded under the medications section.

Please note that homeopathic medications will be coded as MED00227 (see medications section below for details). Herbal medications and alternative medications/therapies should be coded by following the instructions in the medications section below. Use MED00499 to code Physical alternative remedy: acupuncture, acupressure, energy therapies (electromagnetic therapy, Qi gong, Reiki, etc), chiropractic adjustment, aromatherapy, therapeutic massage, etc.

Hospitalizations: This section is in both versions of the TEDDY Book. The mother should record any hospitalizations of the child or emergency room visits here. If the

child has been hospitalized, obtain the parent's permission to review the child's medical record.

Day Care and Other Social Groups: This section is in both versions of the TEDDY Book. In this section, the mother should record those times the child is regularly (once a week or more) around other children, except the child's own siblings. This can be day care or other regular social get-togethers. In the first section, the mother should record if the child is in some kind of day care. It can be at the child's home, with at least one other child that is not a sibling, or outside of the child's home. The mother should also record if there are any changes to the child's day care. For example, the type of day care might change or there might be an increase or decrease in the number of hours the child is in day care. The mother should record the number of children that are in the child's day care group. If the number of children changes from day to day, she can provide the average number of children usually in the child's day care group. Help the mother record any day care experiences the child has had to date. In the next section, help the mother record other social group activities that the child regularly participates in at least once a week, such as a playgroup in someone's home, baby swim classes, etc.

Important Events: This section is in both versions of the TEDDY Book. In this section, the mother records important events in the child's life. For each event, the mother should record the child's age and how the event affected the child and how the event affected the mother. To help the mother's recall of important events, provide her with two lists of events that can happen to parents and children. Remind her that these are just examples. The mother should be encouraged to record all events she considers important to her or the child. Ask her to record any events that have happened to date.

Autoantibody Results (this section is not in the first TEDDY Book for birth-2 years, but can be found in the second TEDDY Book for 2-5 years): If applicable clinic staff will indicate the date of the blood draw, if the child was negative or positive for GADA, IA-2A and/or IAA, and the child's blood glucose level.

Other Things: In this section, encourage the mother to write down important things the mother might want the study staff to know about the child, like behavior, reactions etc.

Next Study Visit (this section is only in the TEDDY Book for birth-2 years): Encourage the mother to use this section to record all questions that might arise between study visits. Remind her that if she has a question that cannot wait until the next study visit, she can call the toll free number and speak to a study staff person at any time.

Teddy Visits: Study staff can use this section to record instructions for the next study visit.

Three Day Food Record Instructions (this section is only in the TEDDY Book for birth-2 years): This section provides "reminder" information for the parent about how to carry out the 3 day food record. Remember to remind the caretaker to save labels and boxes of foods and supplements, and put them in the special pocket of the

TEDDY book that is designed to collect these items, so they will be available to clinic staff on the next TEDDY visit.

Poop Sample Collection: This section provides "reminder" information for the parent about how to collect a stool sample.

After the TEDDY book has been reviewed in detail, remind the mother of the advantages of keeping the TEDDY book up to date. However, tell her that she does not HAVE to fill in the book (i.e., it is not a requirement of the study), but that it is better to record some things than nothing.

11.3 How to register what the mother has recorded in the TEDDY Book.

The information from the TEDDY Book is registered onto the TEDDY Extraction Forms. (See 17.2 on how to download the Extraction Forms). The data is obtained by using the questions and prompts in the Extraction form. Register one subject at a time and start from the beginning of the book. There are two options for registering the data:

1. Register on the Extraction Form. When the recording of data is finished and the Form has been completed with all necessary codes the Extraction Form is scanned, uploaded and sent by Internet to the DCC (see 17.2). All pages of the Extraction Form need to be scanned even though some pages might lack information.

2. Enter the data directly into a computer using the online version of the TEDDY Book extraction form on the TEDDY website. See section 17.1.2. to locate online forms.

The Extraction Form is used for the first time at the 6 month clinic visit. Most of the topics of the TEDDY book are included in the interview at the 3 month clinic visit. When the TEDDY book is introduced to the mother at the 3 month visit the TEDDY book will be filled out together with the mother and the relevant information obtained during the interview will be written in the book as well.

- A black ink pen for completing the extraction form should be used by the clinical staff. Clarity of corrections needs to be a priority.
- Most answers require filling in a circle. Some answers require letters or numbers placed in boxes, staff should follow the same instructions given to parents.
- If an answer is changed, a large X should be drawn across the incorrect response, the staff member making the correction should initial and date next to it and the new answer should be clearly indicated.
- Dates use the European format: day/month/year.
- If a respondent purposefully refuses a question the interviewer should so note on the extraction form, initial and date.

Encourage the mother to bring along the child's health care book/chart to the clinic visit to facilitate the extraction. Also, it might be helpful if the parent brings in empty containers of formulas, vitamins, medicines, etc. to facilitate the extraction.

11.3.1 Before the clinic visit

1. Download the TEDDY Data Extraction Form for the clinic visit from the TEDDY website (see MOO section 17.2).

2. It is best to have the extraction form from the previous visit and/or the TEDDY Book Summary (link to summary can be found at the top of each subject's Participant's Details Page) of data from earlier visits (applies from the 6M visit forward).

Fill in all of the fields in the "office use only" box on the first page of the form.
Note:

- A new TEDDY Book Data Extraction form is used for each visit. Please remember to fill in which visit the extraction form is associated with (6 month, 9 month, etc).
- "Visit Location Code" this is the location where the TEDDY visit took place. Drop-down list based upon TEDDY Clinical Center field.
- "Interview Date" in day/month/year format; this is the date the interview took place).
- "Interviewer" this is the person who conducts the interview with the parent/primary caretaker, the code can be found in the member directory on the TEDDY website.
- "TEDDY Staff Code of Interviewer" this is the person who conducts the interview with the parent/primary caretaker, the code can be found in the member directory on the TEDDY website.

11.3.2 During the clinic visit

The extraction should be done in a relaxed manner in the form of a conversation with the parent(s). At the same time the extraction should be concise and done with the help of the prompts and questions at each page and the headings in the tables. It is important to follow up on items where at an earlier visit it was reported that the child had started something (a formula, a medication, day care etc.), and ask if it has been stopped.

In order to remember which items from the TEDDY Book have been recorded on the Extraction Form at previous visits, the staff member can make a mark or write an initial in the book to the right of the line(s) that has been extracted. Please remember that the TEDDY Book belongs to the child and his/her parents. Therefore avoid making big marks, punching the pages etc.

There are many items in the book that need to be coded. The coding should be done after the visit, but it is important that the interviewer is familiar with the items that should be coded in order to be able to obtain the information needed for doing the right coding.

The extraction
Start from the beginning of the page where the child's early diet is recorded.

1. Child's early diet

a. Breastfeeding - this section can be found in the TEDDY Book for birth-2 years and the TEDDY Book for 2-5 years:

Does the child get any breast milk NOW?

- If the child has ever breast fed, but has now stopped breastfeeding, mark "NO" and record either the date when the child stopped breast feeding or the age of the child when the breastfeeding was stopped (if you have already recorded the stop date or age of the child when breast-feeding stopped on an earlier extraction form, it is only necessary to mark "NO" on the new extraction form, you do not have to fill in the additional information (stop date or age) a second time).
- If the child is exclusively breastfed for a certain period of time and then the breastfeeding is stopped and formula is introduced exclusively for a period of time following a restart of breastfeeding again, we do not record the first stopping date, only the date when the breastfeeding was stopped for good for this child. The bubble chart in the TEDDY book will be used to indicate the months when the child did or did not receive breast milk.
- If the child is currently receiving breast milk, mark "YES", and fill in the bubble of the current age of the infant or child in the provided table.
- If the child was never breast fed, mark "The baby/child was never breast-fed."

b. Infant formula- this section can be found in the TEDDY Book for birth-2 years only; if a child starts a formula during the time of usage of the TEDDY Book for 2-5 year olds the Diet Committee is not interested in collecting this data; if the parent tells you a stop age of a formula during the time of usage of the TEDDY Book for 2-5 year olds you can indicate the stop age on the birth-2 year extraction form:

Is the child given any formula NOW?

- If the infant does <u>not</u> currently receive any formula, even in small amounts, then the "NO" option should be filled in
- If the child is currently given formula, mark "YES" and record the brand name code as well as type of formula the child is given and the age in months of the child when the formula was started.
- Please remember if the child was previously given formula and has stopped since the last visit, you must record the age of the child when the formula was stopped along with the other formula information (formula code, if formula was 'ready to feed', 'powder' or 'liquid concentrate', age of child when formula was started and reason why formula brand/type was changed) on the new extraction form.

  If necessary, the following conversion table will be used to convert the age of the child when formula was started as reported by the mother to what is asked for on the questionnaire for the TEDDY Book birth-2 years.

  Days 0-3 = 0 weeks = 0 months
  Days 4-10 = 1 week = 0.25 month
  Days 11-17 = 2 weeks = 0.50 month
  Days 18-24 = 3 weeks = 0.75 month
  Days 25-31 = 4 weeks = 1 month
  Days 32-38 = 5 weeks = 1.25 months etc...

Encourage the mother to bring empty containers to help identify the item. Use the visual aids provided in the clinic to identify the SPECIFIC BRAND AND TYPE of formula. Major differences exist in baby formula ingredients, even among the same brand. Many formulas are fortified with nutrients such as DHA, an omega-3 fat that is of particular interest to TEDDY. For example, in the USA, list the brand "Enfamil Lipil with Iron," or "Enfamil Lacto Free Lipil with Iron," not just "Enfamil." The "Lipil" in the name indicates the product is fortified with DHA, the important omega-3 fat.

If there are questions, or if there is a formula that is "missing" from the code list, or the visual aids, consult the nutritionist at the clinic site. For more information about recording formula during the dietary interview, see Chapter 12 of the TEDDY Manual of Operations.

If the infant currently receives formula and there is **NO** change in the formula information that was recorded on the TEDDY Book extraction form at a previous visit, then the "YES" option should be marked and the site should not record the same formula information again on the current data extraction form. Please note that this only applies if there is **NO** change in the formula information.

> **Note:** The 3 Month Interview and TEDDY Book extraction form are considered to be two different data collection forms with data being collected differently on each (for example age of child is collected in weeks in the 3 Month Interview and in months in the TEDDY Book extraction form). Therefore if the infant has continuously been given the exact same formula since it was recorded in the 3 Month Interview, this is the **first** TEDDY Book extraction form being completed for the subject and there is NO CHANGE in the formula information that was recorded in the 3 Month Interview, the "YES" option should be marked and **ALL** of the formula data for that particular formula (formula brand name, formula type, age in months of the child when the formula was started) recorded in the 3 month Interview must be re-entered on the first TEDDY Book extraction form.

If there **IS** a change in the formula information from the extraction form that was filled out at the previous visit, the OLD brand name code and type of the formula should be entered with the original start and stop age in months. The reason for the change should also be documented - the reason for changing formula code should be entered in the row that the new formula information is recorded in; it should not be entered in the row with the old formula information. If applicable, all information for the NEW formula should then be recorded and the stop age should be left blank. Please note that the change could be in brand or in the type (ready to feed, powder, or liquid concentrate) of the formula.

2. Introduction of New Food Items - this section can be found in the TEDDY Book for birth-2 years only; if a child is introduced to a new food item during the time of usage of the TEDDY Book for 2-5 year olds the Diet Committee is not interested in collecting this data:
Since the last visit, has the child been given another new food item or something other than breast milk?

- If the child has not been given another new food item or something other than breast milk since the last visit mark "NO".
- If the child has been given another new food item or something other than breast milk since the last visit mark "YES" and fill in the age in months next to the food item in the provided table.

The interviewer should be familiar with the list and the grouping of the items. Only the introduction of new food items should be recorded. Having the previous extraction form or the TEDDY Book Summary print out easily available will help when recording the introduction of new foods (note: foods recorded on the 3 Month Interview will not appear on the TEDDY Book Summary; only foods recorded on the TEDDY Book extraction forms appear on the TEDDY Book summary). It is important to be as specific as possible in identifying brand names and types of food. Use the visual aids in the clinic to help a parent recognize a product by its label. When labels are submitted by parents, read the labels carefully. Sometimes there are ingredients in the foods that are not obvious. For example, there is a brand of baby food popular in the USA known as "Beechnut." The line of products called "Beechnut First Advantage" may contain cream, egg protein, and/or flour, but the line of standard "Beechnut" products usually does not. So the first exposure to dairy or wheat could come from these "hidden" sources and this would be important to know for TEDDY.

3. **Other Diet Choices** this section is in the TEDDY Book for birth-2 years; it is given a new title of All Special Diets and placed after the Allergies section in the TEDDY Book for 2-5 year olds and TEDDY Book for 6-15 year olds data extraction form. Directions below apply to both the Other Diet Choices section and the All Special Diets section. This section needs to be filled in if the child is given a special diet because of allergy to cow's milk, cereal or wheat (other avoidance diets due to allergy do not need to be indicated), celiac disease, cultural beliefs or other reasons.

Is the child on any new diets?

- If the child is not on any new diets mark "NO".
- If the child is on a new type of diet since the previous visit mark "YES" and the type of diet and the start age of the diet should be recorded. Also indicate if the type of diet was recommended by a health care provider or not.
    - For situations in which the start date for an ongoing special diet for a returning family is unknown the start date will be recorded as 6 months before the date of the return visit. Pursuit of medical records is always preferred.
- Please remember that if the child was previously on a diet and has stopped since the last visit, you must record the age of the child when the diet was stopped along with the other diet information (other diet code if applicable, age of child when diet was started and if the diet was recommended by a health care provider or not) on the new extraction form. (If the child is not on any new diets and the only new data you are entering is the age of the child

when the previous diet was stopped, then "NO" should be selected to the question "Is the child on any new diets?".)

- Use radio button "Ended, but end date unknown" for situations in which a special diet is open, but has stopped greater than one year ago and the parent does not know the end date. This can be used for both families who rejoin and families who have never dropped out.
- For situations in which an item is open, but has stopped less than one year ago parent should provide best estimate of stop date. This should be applied for both families who rejoin and families who have never dropped out.
- For situations in which an item is open, but has stopped greater than one year ago and the parent DOES know the end date, TEDDY staff member should record the end date provided by the parent. This should be applied for both families who rejoin and families who have never dropped out.

If necessary, the following conversion table will be used to convert the age of the child when diet was started as reported by the mother to what is asked for on the questionnaire for the TEDDY Book birth-2 years.

Days 0-3 = 0 weeks = 0 months
Days 4-10 = 1 week = 0.25 month
Days 11-17 = 2 weeks = 0.50 month
Days 18-24 = 3 weeks = 0.75 month
Days 25-31 = 4 weeks = 1 month
Days 32-38 = 5 weeks = 1.25 months etc...

If necessary, the following conversion table will be used to convert the age of the child when diet was started as reported by the mother to what is asked for on the questionnaire for the TEDDY Book 2-5 years.

Months 0-0.49 = 0 months
Months 0.50-1.49 = 1 month
Months 1.50-2.49 = 2 months
Months 2.50-3.49 = 3 months
Months 3.50-4.49 = 4 months
Months 4.50-5.49 = 5 months etc . . .

If entering a diet start age with 0 years in the TEDDY Book for 2-5 years, rather than entering 0 just leave the years field blank.

If the child has continuously been on the same type of diet since it was recorded on the TEDDY Book extraction form at a previous visit and there is NO CHANGE in the diet information that was recorded on the extraction form at the previous visit, then "NO" is marked and the site should not record the same diet information again on the current data extraction form (unless a stopped age needs to be indicated). Please note that this only applies if there is **NO** change in the diet information.

Note: The 3 Month Interview and TEDDY Book extraction form are considered to be two different data collection forms with data being collected differently on each (for example age of child is collected in weeks in the 3

Month Interview and in months in the TEDDY Book extraction form). Therefore if the child has continuously been on the same type of diet since it was recorded in the 3 Month Interview, this is the **first** TEDDY Book extraction form being completed for the subject and there is NO CHANGE in the diet information that was recorded in the 3 Month Interview, the "YES" option should be marked and **ALL** of the diet data recorded in the 3 month Interview must be re-entered on the first TEDDY Book extraction form.

If the child was reported to be on a specific type of diet and has stopped the diet since the previous visit, all of the information pertaining to this diet should be recorded again on the new extraction form along with the age of the child when the diet was stopped. (If the child is not on any new diets and the only new data you are entering is the age of the child when the previous diet was stopped, then "NO" should be selected to the question "Is the child on any new diets?".)

If a certain type of food is avoided, the date that the food stopped being given to the child should be recorded in the "Started" column not the date that the symptoms occurred.

4. Allergies- in the TEDDY Book used for birth-2 years this section comes after the Other Diet Choices section and in the TEDDY Book for 2-5 year olds and TEDDY Book for 6-15 year olds data extraction form this section is placed before the All Special Diets section. For both TEDDY Books all allergies should be recorded in the Allergies section, regardless of whether they have been indicated in the Other Diet Choices or All Special Diets section or not (for example if a subject is avoiding cow's milk due to an allergy, this is indicated in the Other Diet Choices section (for the TEDDY Book birth-2 years) or the All Special Diets section (for the TEDDY Book 2-5 years) and it should also be indicated in the Allergies section of that TEDDY Book).

Does the child have any new allergies?

- If the child does not have any new allergies mark "NO".
- If the child does have a new allergy mark "YES" and fill in the information in the provided table.
    - For situations in which the start date for an ongoing allergy for a returning family is unknown the start date will be recorded as 6 months before the date of the return visit. Pursuit of medical records is always preferred.
- Each allergy should only be recorded once. Refer to previous TEDDY Data Extraction forms or the TEDDY Book Summary for past related records.
- Please remember that if the child previously had an allergy and it has stopped since the last visit, you must record the age of the child when the allergy stopped along with the other allergy information (allergy code, age of child when allergy started, allergy symptom codes and health care provider diagnosis) on the new extraction form. (If the child does not have any new allergies and the only new data you are entering is the age of the child when the previous allergy stopped, then "NO" should be selected to the question "Does the child have any new allergies?".)
    - Use radio button "Ended, but end date unknown" for situations in which an allergy is open, but has stopped greater than one year ago and

the parent does not know the end date. This can be used for both families who rejoin and families who have never dropped out.

- For situations in which an item is open, but has stopped less than one year ago parent should provide best estimate of stop date. This should be applied for both families who rejoin and families who have never dropped out.
- For situations in which an item is open, but has stopped greater than one year ago and the parent DOES know the end date, TEDDY staff member should record the end date provided by the parent. This should be applied for both families who rejoin and families who have never dropped out.

If necessary, the following conversion table will be used to convert the age of the child when the allergy started as reported by the mother to what is asked for on the questionnaire for the TEDDY Book birth-2 years.

Days 0-3 = 0 weeks = 0 months
Days 4-10 = 1 week = 0.25 month
Days 11-17 = 2 weeks = 0.50 month
Days 18-24 = 3 weeks = 0.75 month
Days 25-31 = 4 weeks = 1 month
Days 32-38 = 5 weeks = 1.25 months etc...

If necessary, the following conversion table will be used to convert the age of the child when the allergy started as reported by the mother to what is asked for on the questionnaire for the TEDDY Book 2-5 years.

Months 0-0.49 = 0 months
Months 0.50-1.49 = 1 month
Months 1.50-2.49 = 2 months
Months 2.50-3.49 = 3 months
Months 3.50-4.49 = 4 months
Months 4.50-5.49 = 5 months etc . . .

If entering an allergy start age with 0 years in the TEDDY Book for 2-5 years, rather than entering 0 just leave the years field blank.

5. Weight and Length or Height - this section can be found in the TEDDY Book for birth-2 years and the TEDDY Book for 2-5 years and TEDDY Book for 6-15 year olds data extraction form:
Measurements done by a health care provider are recorded here. (The measurement done at the TEDDY visit should be recorded on the Physical Exam Form and not in the TEDDY Book. Refer to the section on Clinical Measures (9.2.2).) Encourage the parent to bring along the child's chart and record the measurements. The weight should be registered in pounds and ounces for the US sites and in kilograms for the European sites. The length should be registered in inches for the US sites and in centimeters for the European sites.

6. Vaccinations - this section can be found in the TEDDY Book for birth-2 years and the TEDDY Book for 2-5 years and TEDDY Book for 6-15 year olds data extraction form:
Has the child been given any vaccinations since the last TEDDY visit?

- If the child has not been given any vaccinations since the last visit mark "NO".
- If the child has been given a vaccination(s) since the last visit mark "YES" and fill in the information in the provided table.

Encourage the parent to bring in the vaccination record of the child; when the parent brings in the vaccination card to the TEDDY visit the site should make a copy of the card for the child's TEDDY records. The date should be recorded each time a vaccination is given. If the child has received a booster since the previous visit fill in the date of the booster in the column of the booster received. Note: there is more than one extraction page for this section in both TEDDY Books.

If it is known that a combination vaccination (a vaccination with more than one component, such as Pediarix which is Diphtheria + Tetanus + Pertussis (Whooping Cough) + Hepatitis B + Polio) was administered to the subject, the vaccination should be coded with one individual code rather than making a data entry for each of the vaccination's components. For example, if it is known that Pediarix was administered the site should use code V0031.

If it is not known whether the subject was given a combination vaccination or individual vaccinations, each of the vaccinations' components should be coded separately.

> **Note:** If at a TEDDY visit a parent indicates that a child was given vaccinations, but does not know if the child was given a combination vaccination or not, as stated above the TEDDY staff member should code each vaccination component individually in the TEDDY Book extraction form. Then if at a future time the site receives the vaccination record from the doctor and the record indicates that the vaccination was indeed given in combination form, it has been decided that the site should not change the original entries of the individual components recorded on the extraction form and that the site should not code the combination vaccination on the new extraction form.

Country-specific guidelines for coding of Pneumococcal Conjugate Vaccines (PCV)

- US:
  - For PCV administered from March – June 2010 any of the following codes will be accepted: V0053: Unknown type of Pneumococcal vaccine; V0013: Pneumococcal conjugate vaccine (PCV7); or V0052: Pneumococcal conjugate vaccine (PCV13). This time period is considered to be the transition time from PCV7 to PCV13.
  - For PCV administered before March 2010: V0013: Pneumococcal conjugate vaccine (PCV7) should be used.
  - For PCV administered after June 2010: V0052: Pneumococcal conjugate vaccine (PCV13) should be used.
- Finland:
  - The Pneumococcal vaccination was added to the national vaccination program in 2010. All babies born on or after June 1,

2010 have been eligible to get free pneumococcal conjugate vaccines PCV10. i.e., TEDDY babies have NOT been vaccinated according to this program. Many TEDDY babies have been vaccinated but it is difficult to collect information now on what kind of vaccination each of them has received:
    - Many parents have bought a vaccine for their baby which could have been either PCV7, PCV10 or PVC13.
    - Many parents have reported only "Pneumococcal vaccine", without any commercial name of the vaccine.
    - Many of the TEDDY babies belong to the Pneumococcal Vaccine studies. At least one of these studies is still going on and the code has not been opened yet.
  - Our Study Nurses have recorded the name of the vaccine whenever it has been marked on the child's vaccination card or the parents have provided some other reliable information of the vaccine. If the name is available we can then check which vaccine was given to the child.
- Germany:
  - Should have the documentation to go with the appropriate code - will use either code V0013: Pneumococcal conjugate vaccine (PCV7); or V0052: Pneumococcal conjugate vaccine (PCV13)
  - There will be some instances in which the specific vaccine will be unknown and V0053: Unknown type of Pneumococcal vaccine will be used, but for the most part the above applies.

- Sweden:
  - PCV10 started being administered in Sweden in February 2010, however as of December 2011 very few children had received this vaccine. PCV7 was still widely being used as of December 2011 due to the large number of remaining supplies.

7. Multivitamins, Single Vitamins, Minerals, and Other Dietary Supplements this section can be found in the TEDDY Book for birth-2 years and the TEDDY Book for 2-5 years and TEDDY Book for 6-15 year olds data extraction form:

All dietary supplements given to the child should be recorded in the dietary supplements section, except pure homeopathic products and pure herbal products and those supplements listed in the “Do Not Code” section of the “Diet TEDDY Coding Decisions” document which can be found under the Diet Committee section of the TEDDY website. Dietary supplements taken for a medical condition/illness should be entered in the dietary supplements section of the extraction form, not in the medications section (this includes products such as Tums and Rolaids whose active ingredients consist only of vitamins, minerals and/or other dietary supplements). Encourage the mother to bring in packages.

> **Note:** The Diet Committee is not interested in pure homeopathic products. Sites should review the complete ingredient list of the product before classifying it as purely homeopathic. If the product contains added vitamins, minerals probiotics, etc then it should be coded in the dietary supplements section. If the product is deemed to be purely homeopathic, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken

for a medical condition then it should be coded under the medications section. A homeopathic product can be identified by label. Doses for homeopathic products have the Roman numeral listed in the recommended doses, with a C, M, or X, such as 6X, 12C, 5M, etc. In Europe and some other parts of the world you will see the letter D or DH. This refers to decimal or 1/10 which is the same as X, used in the U.S. Also in Europe the position of the number and letter designation are reversed from the US designation. So you will see such designations as D5 or D10 which are equivalent to 5X and 10X. You will also encounter CH and CK, these are equivalent to C, referring to the Centesimal or 1/100 dilution rate.

The Diet Committee is not interested in pure herbal products. Sites should review the complete ingredient list of the product, before classifying it as purely herbal. If the product contains added vitamins, minerals, probiotics, etc then it should be coded in the dietary supplements section. If the product is deemed to be purely herbal, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken for a medical condition then it should be coded under the medications section.

Note: Given the possibility of product reformulation over the course of TEDDY, the clinic will need to request a new supplement code whenever a reformulation is noticed. The site and/or the DCC will contact the manufacturer to find out the time of reformulation and the DCC will include this date in the code details of the reformulated product as well as the old product.

When requesting new dietary supplement codes, US sites should be sure to submit the Supplement Code Request Form along with their code request to the DCC.

Has the child been given any NEW single vitamins, multivitamins, multiminerals, or other dietary supplements since the last visit?

- If the infant has not been given any new dietary supplements since the last visit then the "NO" option should be filled in.
- If the child has been given a new dietary supplement since the last visit, mark "YES" and record the type and the brand of the preparation, the amount given, the number of times per week it is given, and the age (in months for recordings in the TEDDY Book for birth-2 years and in years and months for the TEDDY Book for 2-5 years) of the child in which the supplement was started.
    - For situations in which the start date for an ongoing dietary supplement for a returning family is unknown the start date will be recorded as 6 months before the date of the return visit. Pursuit of medical records is always preferred.
- Please remember that if the child was previously given dietary supplements and has stopped since the last visit, you must record the age of the child when it was stopped along with the other dietary supplement information (dietary supplement code, the number of drops, droppers, mL, tablets or other form given to the child, the number of times the supplement was given to the child per week and the age of the child when the supplement was started) on the new extraction form. (If the child is not on any new dietary supplements and the only new data you are entering is the age of the child when the previous

dietary supplement was stopped, then "NO" should be selected to the question "Has the child been given any NEW single vitamins, multivitamins, multiminerals, or other dietary supplements since the last visit?".)

- Use radio button "Ended, but end date unknown" for situations in which a dietary supplement is open, but has stopped greater than one year ago and the parent does not know the end date. This can be used for both families who rejoin and families who have never dropped out.
- For situations in which an item is open, but has stopped less than one year ago parent should provide best estimate of stop date. This should be applied for both families who rejoin and families who have never dropped out.
- For situations in which an item is open, but has stopped greater than one year ago and the parent DOES know the end date, TEDDY staff member should record the end date provided by the parent. This should be applied for both families who rejoin and families who have never dropped out.

If necessary, the following conversion table will be used to convert the age of the child when supplement was started as reported by the mother to what is asked for on the questionnaire for the TEDDY Book birth-2 years.

Days 0-3 = 0 weeks = 0 months
Days 4-10 = 1 week = 0.25 month
Days 11-17 = 2 weeks = 0.50 month
Days 18-24 = 3 weeks = 0.75 month
Days 25-31 = 4 weeks = 1 month
Days 32-38 = 5 weeks = 1.25 months etc...

If necessary, the following conversion table will be used to convert the age of the child when supplement was started as reported by the mother to what is asked for on the questionnaire for the TEDDY Book 2-5 years.

Months 0-0.49 = 0 months
Months 0.50-1.49 = 1 month
Months 1.50-2.49 = 2 months
Months 2.50-3.49 = 3 months
Months 3.50-4.49 = 4 months
Months 4.50-5.49 = 5 months etc . . .

If entering a supplement start age with 0 years in the TEDDY Book for 2-5 years, rather than entering 0 just leave the years field blank.

If the child has been continuously given the same dietary supplement since it was recorded on the TEDDY Book extraction form at a previous visit and there is NO CHANGE in the dietary supplement information that was recorded on that extraction form, then "NO" is filled in and the site should not record the same dietary supplement information again on the current data extraction form (unless a stopped age needs to be indicated). Please note that this only applies if there is **NO** change in the dietary supplement information.

Note: The 3 Month Interview and TEDDY Book extraction form are considered to be two different data collection forms with data being collected differently on each (for example age of child is collected in weeks in the 3 Month Interview and in months in the TEDDY Book extraction form). Therefore if the child has been continuously given the same dietary supplement since it was recorded in the 3 Month Interview, this is the **first** TEDDY Book extraction form being completed for the subject and there is NO CHANGE in the supplement information that was recorded in the 3 Month Interview, the "YES" option should be marked and **ALL** of the supplement data recorded in the 3 month Interview must be re-entered on the first TEDDY Book extraction form.

If the child is no longer receiving the supplement as recorded at the previous visit, all of the information pertaining to the dietary supplement should be recorded again on the new extraction form along with the age of the child when the dietary supplement was stopped. (If the child is not on any new dietary supplements and the only new data you are entering is the age of the child when the previous dietary supplement was stopped, then "NO" should be selected to the question "Has the child been given any NEW single vitamins, multivitamins, multiminerals, or other dietary supplements since the last visit?".)

8. Illnesses- this section can be found in the TEDDY Book for birth-2 years and the TEDDY Book for 2-5 years and TEDDY Book for 6-15 year olds data extraction form:

8a. Acute Illnesses: Has the child been ill since the last visit? On February 6, 2015 the following probe was added to the TEDDY Book data extraction form "*This could be an illness with a fever, any infection, a virus, or other common childhood conditions like pinworms or lice."*

- If the child has not been ill since the last visit mark "NO".
- If the child has been ill since the last visit mark "YES" and fill in the information in the provided table. For each illness, indicate the date of the illness, the symptoms (symptoms should always be recorded; for rare situations in which there are no symptoms, a radio button is available on the extraction form to indicate this), whether the child had a fever (please note that TEDDY defines a fever as a temperature equal to or higher than 38°C or 101°F), if the child did have a fever whether it was measured or not, the diagnosis (if applicable) and whether or not the illness was diagnosed by the parent or health care provider. Symptoms should always be recorded, however there may not always be a diagnosis, so diagnosis may be left blank sometimes.

  Note: For data analyses completed on fevers (a temperature equal to or higher than 38°C or 101°F) the answer indicated in the column entitled "Fever? (temperature is equal to or higher than 38°C or 101°F)" will be used. Therefore it is important for the site to be sure to always provide an answer for this question on the data extraction form when an illness is indicated.

  After discussion amongst the Coordinators it has been discovered that sites are indicating fevers differently on the TEDDY Book extraction

forms (listed below is how each site is recording this data). It has been decided that as long as an answer is indicated in the column entitled "Fever? (temperature is equal to or higher than 38°C or 101°F)" the data entry methods listed below are both acceptable.

Indicate answer to "Fever? (temperature is equal to or higher than 38°C or 101°F)" AND indicate fever as a symptom:
Sweden
Finland

Indicate answer to "Fever? (temperature is equal to or higher than 38°C or 101°F)", but DO NOT indicate fever as a symptom (if no other symptoms they indicate "No symptoms"):
Colorado
Georgia/Florida
Washington
Germany

Note: If an illness diagnosis is made, whether it is made by the parent or the health care provider, the diagnosis code should always be indicated in the illness question. If diagnosed by the health care provider then this option should be marked, if diagnosed by the parent then this option should be marked. If either 'diagnosed by parent' or 'diagnosed by health care provider' is marked a diagnosis code must be indicated. If there is no diagnosis then neither 'diagnosed by parent' nor 'diagnosed by health care provider' should be indicated.

Note: In the Diagnosis column of the Illness question two answer choice options are provided: one for "Diagnosed by parent" and one for "Diagnosed by health care provider". If the healthcare provider does not physically see the child to make the diagnosis (for example the diagnosis is made by the parent describing the symptoms over the phone to the health care provider's office) then the choice "Diagnosed by parent" should be chosen. The choice "Diagnosed by health care provider" should only be selected when the health care provider physically sees the child.

Note: When specific symptoms result in multiple diagnoses each diagnosis and all associated data (illness date, symptom(s) and fever information) should be indicated on a separate data row on the extraction form.

In the TEDDY book, there is a list of illnesses and symptoms. The list is not complete, but suggests symptoms to be observed by the parents.

Standard probes have been developed for several of the illnesses and symptoms to help with the ICD- 10 coding later.

Diarrhea

TEDDY book reviewer needs to determine if the diarrhea was more likely to be infectious or non-infective gastroenteritis.

The more "yes" answers to the following questions, the more likely it is that the diarrhea was caused by something infectious:

1) Did any of the rest of the family have diarrhea around the same time?
2) Did he/she have a fever at the same time?
3) Was there any vomiting with the diarrhea?

If "yes" to all/most (do we want to say any?) of above, then we will code as diarrhea, presumed infectious (A09). If "no" to all/most of above, code as diarrhea, noninfective gastroenteritis (K52.9)

Skin Infection/Condition

The recommendation for this is that we only code a specific illness such as impetigo, chicken pox, eczema, etc. if the parent informs us that this is what baby has/had. When they mark "skin infection" in their TEDDY book, we should ask if this condition was assessed by a health care provider. The answer should be there in the book. If they answer yes, and that the provider told them it was eczema or an abscess, or a reaction to a perfumed detergent, or whatever, we code as such. If they do not know what the skin condition is/was, we code R21 for rash unspecified (if parent describes condition as a rash) or L08.9 for local infection of skin and subQ tissue, unspecified if parent describes the condition as an infection.

The more "yes" answers to the following questions, the more likely the condition was an infection:

1) Was there any pus associated with the eruptions?
2) Were the sores crusty, weeping, or honey colored?
3) Did the condition respond to antibiotics (if given)?
4) Did the condition begin with a scratch, a splinter, a puncture or a bug-bite (anything that broke the skin) and then worsen?

Note: if determined the condition was likely an infection, but the parent does not specify, we code as cellulitis, unspecified (L03.9)

The more "yes" answers to the following questions, the more likely the condition was NOT an infection:

1) Was the area scaly?
2) Was the area itchy?

Poor Appetite/Fussy Baby

Fussy Baby: We are trying to probe for inconsolable crying as an indication of an infection. "Fussy baby" means baby is crying, and cannot be consoled, even though all his/her comforts have been looked after. In other words, baby has a clean diaper, is neither hot nor cold, is not hungry, has been held and cuddled, etc. The "fussiness" must last for at least a day, and does not follow a pattern, like colic often does. For example, if the baby cries for several hours a night every night, this is not what we want to extract, as it is probably

not due to an infection. The inconsolable crying we are looking to capture is usually associated with or followed by some other sign of infection (vomiting, fever, diarrhea, etc.). If mom has indicated "fussy baby" and it does not fit the above description, we recommend not extracting it, as it is unlikely to be related to T1D.

Poor appetite: This is non-specific indication that the child is sick or getting sick, so we are looking for changes in the child's feeding pattern, where they suddenly have a drop in intake. Like "fussy baby", we generally want to code for this if it is a noticeable change in feeding behavior and is associated with or followed by some sign of illness or infection (vomiting, fever, diarrhea, etc.).

8b. Chronic Illnesses: Since the last visit, has your child been diagnosed by a health care provider with any chronic illness or condition?

- If the child has not been diagnosed by a health care provider with any chronic illness or condition since the last visit mark "NO".
- If the child has been diagnosed by a health care provider with any chronic illness or condition since the last visit mark "YES" and fill in the information in the provided table. For each chronic illness, indicate the name of the chronic illness/condition and the associated ICD-10 code, the date of diagnosis (month and year) by a health care provider and if applicable the date the chronic illness went into remission (month and year).
    - For situations in which the start date for an ongoing chronic illness for a returning family is unknown the start date will be recorded as 6 months before the date of the return visit. Pursuit of medical records is always preferred.
- Please remember that if the child previously had the chronic illness or condition and it has went into remission since the last visit, you must record the date of remission (month and year) along with the associated ICD-10 code and date of diagnosis (month and year) on the new extraction form. (If the child doesn't have any other new chronic illnesses or conditions since the last visit and the only new data you are entering is the date of remission, then "NO" should be selected to the question "Since the last visit, has your child been diagnosed by a health care provider with any chronic illness or condition?")
    - Use radio button "Ended, but end date unknown" for situations in which a chronic illness is open, but has stopped greater than one year ago and the parent does not know the end date. This can be used for both families who rejoin and families who have never dropped out.
    - For situations in which an item is open, but has stopped less than one year ago parent should provide best estimate of stop date. This should be applied for both families who rejoin and families who have never dropped out.
    - For situations in which an item is open, but has stopped greater than one year ago and the parent DOES know the end date, TEDDY staff member should record the end date provided by the parent. This should be applied for both families who rejoin and families who have never dropped out.

A section to record data on chronic illnesses is available on both versions of the TEDDY Book extraction forms; there is not a separate section for chronic illnesses in the TEDDY Book for the parents. The reason that a separate section has not been provided in the TEDDY Book for parents to record chronic illnesses is because it may be confusing to some parents on how to differentiate between acute and chronic illnesses, therefore it has been decided that the TEDDY staff member should probe the parent for this information and record the illness in the correct section of the TEDDY Book extraction form. A chronic illness has been defined for TEDDY as: "A condition generally lasting 3 months or longer. It is permanent, long lasting or results in residual disability. A chronic disease can also be recurrent and relapse repeatedly with periods of remission". If a child is free of symptoms and signs of a chronic disease (for example infectious asthma, epilepsy, atopic eczema) for 2 years staff member should indicate a stop date for the disease. Examples of chronic illnesses of varying severity include: Asthma, Eczema, Rheumatological diseases, Cancer, Hematological conditions (such as bleeding disorders, chronic ITP etc), Epilepsy, Endocrine disorders (such as Diabetes, Autoimmune Thyroiditis, Addisson's Disease, GH-deficiency), Neurological conditions (such as Cerebral Palsy, Multiple sclerosis, varying chronic progressive neurological conditions), Gastroenterological conditions (such as Celiac Disease, Inflammatory Bowel Disease, Crohn's Disease), Congenital heart defects, Malformations, Metabolic disorders.

9. Medications- this section can be found in the TEDDY Book for birth-2 years and the TEDDY Book for 2-5 years and TEDDY Book for 6-15 year olds data extraction form:

Has the child been given any medications - any kind of prescription medication (oral, topical, injection, etc.) and/or oral "over the counter" medication, since the last visit? NOTE: Do not include vitamins and other dietary supplements here.

- If the child has not been given any medications since the last visit mark "NO".
- If the child has been given medication since the last visit mark "YES" and fill in the information in the provided table.
    - For situations in which the start date for an ongoing medication for a returning family is unknown the start date will be recorded as 6 months before the date of the return visit. Pursuit of medical records is always preferred.
- Please remember that if the medication was marked as "ongoing" on previous extraction forms, an inquiry should be made at future TEDDY visits to determine if the child is still given the medication. If the child has stopped taking the medication, remember to record the number of days the child was given the medication along with the other medication information (medication code, reason for taking medication code and age of child when medication was started) on the new extraction form. (In this type of situation since the question asks "Has the child been given <u>any</u> medications . . .since the last visit?", site should mark "YES" to the question when entering the number of days an ongoing medication had been given for.)
    - Use radio button "Ended, but end date unknown" for situations in which a medication is open, but has stopped greater than one year ago and the parent does not know the end date. This can be used for both families who rejoin and families who have never dropped out.
    - For situations in which an item is open, but has stopped less than one year ago parent should provide best estimate of stop date. This should

be applied for both families who rejoin and families who have never dropped out.

- For situations in which an item is open, but has stopped greater than one year ago and the parent DOES know the end date, TEDDY staff member should record the end date provided by the parent. This should be applied for both families who rejoin and families who have never dropped out.

If necessary, the following conversion table will be used to convert the age of the child when medication was started as reported by the mother to what is asked for on the questionnaire for the TEDDY Book birth-2 years.

Days 0-3 = 0 weeks = 0 months
Days 4-10 = 1 week = 0.25 month
Days 11-17 = 2 weeks = 0.50 month
Days 18-24 = 3 weeks = 0.75 month
Days 25-31 = 4 weeks = 1 month
Days 32-38 = 5 weeks = 1.25 months etc...

If necessary, the following conversion table will be used to convert the age of the child when medication was started as reported by the mother to what is asked for on the questionnaire for the TEDDY Book 2-5 years.

Months 0-0.49 = 0 months
Months 0.50-1.49 = 1 month
Months 1.50-2.49 = 2 months
Months 2.50-3.49 = 3 months
Months 3.50-4.49 = 4 months
Months 4.50-5.49 = 5 months etc . . .

If entering a medication start age with 0 years in the TEDDY Book for 2-5 years, rather than entering 0 just leave the years field blank.

- If a medication that has been indicated as being given “as needed” is stopped, the site does not need to have the family attempt to estimate the number of days that the medicine was given. The answer to the number of days the medication was given should remain as “as needed”.
- If parent indicates that a medication was given for a specific number of days and then was given on an “as needed” basis – the medication information along with the number of days that the medication was given should be recorded on one row of the form and the medication information along with the “as needed” indication should be recorded on a separate row of the form.
- If parent indicates that the same medication was given several times since the last visit on an as needed basis, the site should only indicate this once on the data extraction form to cover the entire period of multiple “as needed” administrations.

If the child has been continuously given the same medication since it was recorded on the TEDDY Book extraction form at a previous visit and there is NO CHANGE in the medication information that was recorded on that extraction form, then "YES" is filled in and the site should not record the same medication information again on the current data extraction form. Please note that this only applies if there is **NO** change in the medication information.

Note:

- The 3 Month Interview and TEDDY Book extraction form are considered to be two different data collection forms with data being collected differently on each (for example age of child is collected in weeks in the 3 Month Interview and in months in the TEDDY Book extraction form for birth-2 years). Therefore if the child has been continuously given the same medication since it was recorded in the 3 Month Interview, this is the **first** TEDDY Book extraction form being completed for the subject and there is NO CHANGE in the medication information that was recorded in the 3 Month Interview, the "YES" option should be marked and **ALL** of the medication data recorded in the 3 month Interview must be re-entered on the first TEDDY Book extraction form.

If the child is no longer receiving the medication as recorded at the previous visit, all of the information pertaining to the medication should be recorded again on the new extraction form along with the number of days that the medication was given. (In this type of situation since the question asks "Has the child been given any medications . . .since the last visit?", site should mark "YES" to the question when entering the number of days an ongoing medication had been given for.)

If the same medication is given to the child during different periods of time, each episode should be recorded.

If there is more than one reason for why the medication was given to the child use the next row: fill out all of the information again – codes, ages, etc., enter the 2nd reason why the medication was given to the child and mark "Additional reason for medication above" (if you have a third reason then follow the same process in the next available row, etc).

All pure homeopathic products given for a medical condition should be coded as MED00227. Sites should review the complete ingredient list of the product before classifying it as purely homeopathic. If the product contains added vitamins, minerals probiotics, etc then it should be coded in the dietary supplements section. If the product is deemed to be purely homeopathic, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken for a medical condition then it should be coded under the medications section. A homeopathic product can be identified by label. Doses for homeopathic products have the Roman numeral listed in the recommended doses, with a C, M, or X, such as 6X, 12C, 5M, etc. In Europe and some other parts of the world you will see the letter D or DH. This refers to decimal or 1/10 which is the same as X, used in the U.S. Also in Europe the position of the number and letter designation are reversed from the US designation. So you will see such designations as D5 or D10 which are equivalent to 5X and 10X. You will also

encounter CH and CK, these are equivalent to C, referring to the Centesimal or 1/100 dilution rate. If the pure homeopathic preparation is being given to alleviate symptoms associated with a condition that can be defined by an ICD-10 code, the name of the homeopathic (if known) along with indication that it is a homeopathic preparation should be written under "name of medication", the reason that it was given, the age of the infant (in months for recordings in the TEDDY Book for birth-2 years and in years and months for the TEDDY Book for 2-5 years) when he/she received the medication, and the number of days the preparation was given should also be recorded.

Sites should review the complete ingredient list of the product before classifying it as purely herbal. If the product contains added vitamins, minerals, probiotics, etc then it should be coded in the dietary supplements section. If the product is deemed to be purely herbal, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken for a medical condition then it should be coded under the medications section. A purely herbal product that is given for a medical condition will be assigned a TEDDY medication code based upon its active ingredients. When requesting a medication code for a purely herbal medication, coordinators should provide the DCC with as many of the active ingredients contained in the herbal medication as possible. If none of the active ingredients are able to be identified, then the herbal medication should be coded as "MED00303 - nonspecific herbal medication". If all or a portion of the active ingredients can be identified, the coordinator should send a medication code request to the DCC along with the list of active ingredients

Use MED00499 to code Physical alternative remedy: acupuncture, acupressure, energy therapies (electromagnetic therapy, Qi gong, Reiki, etc), chiropractic adjustment, aromatherapy, therapeutic massage, etc.

An alternative medication/therapy (such as colloidal silver, chelation, etc.) will be assigned a TEDDY medication code based upon its active ingredients. When requesting a code for an alternative medication/therapy, coordinators should provide the DCC with as many of the active ingredients contained in the alternative medication/therapy as possible. If none of the active ingredients are able to be identified, then the alternative medication/therapy should be coded as "MED00525 - nonspecific alternative medication/therapy". If all or a portion of the active ingredients can be identified, the coordinator should send a medication code request to the DCC along with the list of active ingredients.

If a topical medication is used on the child, the interviewer should prompt the parents for whether the topical medication was prescribed by the health care provider. If the topical medication was prescribed, it should be recorded on the TEDDY Extraction Form with the reason for the topical medication, the age of the child and the number of days the child received the topical medication. **Over the counter topical medications should not be recorded; only information on oral over the counter mediations should be collected.**

Dietary supplements taken for medical conditions/illnesses should <u>not</u> be entered in the medication section of the extraction form. Instead they should be entered in the dietary supplements section of the extraction form.

Note: The Diet Committee is not interested in pure homeopathic products. Sites should review the complete ingredient list of the product before classifying it as purely homeopathic. If the product contains added vitamins, minerals probiotics, etc then it should be coded in the dietary supplements section. If the product is deemed to be purely homeopathic, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken for a medical condition then it should be coded under the medications section. A homeopathic product can be identified by label. Doses for homeopathic products have the Roman numeral listed in the recommended doses, with a C, M, or X, such as 6X, 12C, 5M, etc. In Europe and some other parts of the world you will see the letter D or DH. This refers to decimal or 1/10 which is the same as X, used in the U.S. Also in Europe the position of the number and letter designation are reversed from the US designation. So you will see such designations as D5 or D10 which are equivalent to 5X and 10X. You will also encounter CH and CK, these are equivalent to C, referring to the Centesimal or 1/100 dilution rate.

The Diet Committee is not interested in pure herbal products. Sites should review the complete ingredient list of the product before classifying it as a pure herbal product. If the product contains added vitamins, minerals, probiotics, etc then it should be coded in the dietary supplements section. If the product is deemed to be purely herbal, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken for a medical condition then it should be coded under the medications section.

When a parent indicates that an unknown medication was given to the child the site should probe the parent to try to obtain the class or type of medication that was given, for example "unknown antibiotic", "unknown steroid", etc (since the reason the medication was given will be indicated with the ICD-10 code(s)). If the parent does not know this type of information and all the parent knows is that some type of medication was given for X illness/condition, then the site can use the corresponding code for "unknown medication for X illness/condition".

When coding for a medication given for a surgical procedure use the ICD-10 code for the reason why the procedure was done. For example if a child received propofol for the sedation during an ear tube placement procedure, the ICD-10 code that applies to the reason why the tubes were replaced should be used to indicate the reason why the medication was given, such as "H66.9 - otitis media, unspecified".

10. Hospitalizations of the Child- this section can be found in the TEDDY Book for birth-2 years and the TEDDY Book for 2-5 years and TEDDY Book for 6-15 year olds data extraction form:
Has the child been in the hospital since the last visit?

- If the child has not been hospitalized, has not had to go to the ER or had outpatient treatment since the last visit, mark "NO".
- If the child has been hospitalized, had to go to the ER or had outpatient treatment since the last visit, mark "YES" and fill in the information in the provided table.

Record the date that the child was taken to the hospital, this includes emergency room visits in which the child did not stay in the hospital. Document the number of nights

the child stayed in the hospital or indicate that it was an ER visit or outpatient treatment, the name of the facility, and the reason for the hospitalization.

For each time the child has visited the hospital or the emergency room, the parents should be asked if we can access the medical record. If the parents agree, they have to sign an authorization form. If the parents refuse the request, don't ask them again for an authorization. The authorization is obtained only in case we might need to look at the hospital records.

When coding for a surgical procedure use the ICD-10 code for the reason why the procedure was done. For example if a child had an ear tube placement procedure done the ICD-10 code that applies to the reason why the tubes were replaced should be used, such as "H66.9 - otitis media, unspecified".

Circumcision should NOT be coded as a surgery.

If there is more than one reason for why the child was hospitalized use the next row (and also fill out all of the information again – codes, date, number of nights hospitalized, etc) to enter the 2nd reason why the child was hospitalized (if you have a third reason then follow the same process in the next available row, etc).

If the parents give information that is not readily possible to record there are lines for comments in the bottom of the page. This information will not be registered as data, but can be kept as a reminder for the next visit.

11. Day Care and Other Social Groups - this section can be found in the TEDDY Book for birth-2 years and the TEDDY Book for 2-5 years; in the TEDDY Book for 6-15 year data extraction form the section changes to "School or Other Activity Groups" – see instructions for this in section 11.4 below for "TEDDY Calendar and TEDDY Notes Booklet":
Is the child at the present time in a NEW day care situation that includes at least 1 other child, who is not a sibling, or has anything changed in the day care situation since the last visit? or Does the child regularly participate in a NEW group activity with other children, who are not the child's siblings?

- If the child is not in a new daycare or group activity, then mark "NO".
- If the child has started a new daycare or group activity since the last TEDDY visit, then mark "YES" and record the date that the daycare/group activity started, the type of day care/group activity, the number of hours per week attended and the total # of children in the day care/group..
- Please remember that if the child was previously enrolled in a daycare situation or group activity and has stopped since the last TEDDY visit, you must record the stop date along with the other daycare/group activity information (date started, daycare/group activity code, hours per week attended and number of children in group/class) on the new extraction form. (If the child has not started a new daycare or group activity and the only new data you are entering is the date the child stopped attending the previous daycare or group activity, then "NO" should be selected to the question "Is the child at the present time in a NEW day care situation that includes at least 1 other child, who is not a sibling, or has anything changed in the day care

situation since the last visit?" or "Does the child regularly participate in a NEW group activity with other children, who are not the child's siblings?"

If the child has been continuously enrolled in the same daycare or group activity since it was recorded on the TEDDY Book extraction form at a previous visit and there is NO CHANGE in the daycare or group activity, then "NO" is marked and the site should not record the same day care/group activity information again on the current TEDDY Book data extraction form (unless a stopped date needs to be indicated). Please note that this only applies if there is **NO** change in the day care/group activity information.

If there is any change in the daycare/social group situation as recorded at the previous visit, including type of daycare/social group, number of children in the group, the number of hours attended per week, then all of the information pertaining to the daycare/social group should be recorded again on the new TEDDY Book extraction form along with the new information (that has changed since the last visit).

Lapses in day care/social group attendance of greater than or equal to 1 month need to be indicated on the TEDDY Book extraction form. Thus if the child does not attend the day care or social group for periods of time less than 1 month, the lapse in attendance does not need to be recorded.

Ask the parent to estimate or give a range of the number of children in the group if it is not a set number of children. Register the midpoint (for example, if the parent has recorded 4-6 children, write 5 in the Extraction Form). Include the TEDDY child in the total number of children in the group.

If a child starts first grade while TEDDY Book 2-5 year extraction form is still being administered: The constraint for question #10 (Daycare) on the TEDDY Book 2-5 year Data Extraction Form has been changed so that the type of daycare code field now allows sites to enter SC codes (Level or grade of school codes) in addition to the SG and DC codes.

Register other social get-togethers in the same way as day care activities.

In the bottom of the page for Day Care as well as Social Groups are lines for comments. This information will not be registered as data, but can be kept as a reminder for the next visit.

A Camp/other short term activity question was added as part of the "Other Activity Groups" question in the TEDDY Book for 6-15 year olds:
Has the child attended camp or other short term activity since the last visit?

- If the child has not attended camp or other short term activity since the last visit, then mark "NO".
- If the child has attended camp or other short term activity since the last TEDDY visit, then mark "YES" and record the date that the camp/other short term activity started, the date that the camp/other short term activity ended, the type of camp (these will be coded with the "SG" TEDDY codes), indicate the number of days and for day camp indicate hours per day or if it was an

overnight camp mark the radio button (hours per day will be assumed to be 24 hours).

- NOTE: if at the time of the TEDDY visit the camp/short term activity is still ongoing, record the date that the camp/other short term activity started, the type of camp (coded with the "SG" TEDDY code) and hours per day. Once the camp/short term activity has ended, record the date that the camp/other short term activity started, the date that the camp/other short term activity ended, the type of camp (coded with the "SG" TEDDY code), indicate the number of days and for day camp indicate hours per day.

12. Parent and Child Life Experiences- this section can be found in the TEDDY Book for birth-2 years and the TEDDY Book for 2-5 years and the TEDDY Book for 6-15 years data extraction form:

Did you have any of these experiences since we saw you last? Has your child had any of these experiences since we saw you last? Did anything else happen that is not on the list?

- If the parent or child has not had any significant life experiences since the last visit mark "NO".
- If the parent or child has had a significant life experience(s) since the last visit mark "YES" and fill in the information in the provided table.
- From the 10 year visit and on for the life experiences reported by the child there is also an option of "Not Done" for when the child is not able to be interviewed.

Parent and child life experiences that are reported by the parent are recorded in the same table of the TEDDY Book extraction form (tables underneath question # 10a and #10b). Beginning at the 10 year visit the child will also begin to be asked directly about life experiences that have occurred in his/her life; the child reported life experiences will be recorded in a separate table from the parent reported parent and child life experiences on the TEDDY Book extraction form (tables underneath question #10c).

First record the mother's life experiences. If father is the primary caretaker, his experiences should be recorded.

1. Give the mother the card with the list of Parent Life Experiences. Ask if the mother has had any of the experiences on the list since the last clinic visit. If she reports an event listed, write the number of the event and ask according to the headings in the table (Child's age (in months for recordings in the TEDDY Book for birth-2 years and in years and months for recordings in the TEDDY Book for 2-5 years), impact on mother and child). Then ask if something else has happened to her that is not on the list but she considers important and had an impact on her, the child or on both of them. Specify what event(s) and code after the visit. Write 21, the number for parent other event, in the table and ask about the impact of the event. If the mother reports two "other events" specify the second event and write 22, the second number for parent other event, in the table and ask about impact. 34-38 are also available for use if the parent reports more than two "other events". If the mother reports that an event is continuous, document the age of the child (in months for recordings in the TEDDY Book for birth-2 years and in years and months for recordings in the TEDDY Book

for 2-5 years) when the events first began and then mark the continuous life event field.

2. Give the mother the card with a list of Child Life Experiences – please note that there are two versions of the Child Life Experiences list: one list to use through the 5 year 9 month visit and one for school age children that should start being used at the 6 year visit and used for the parent reporting through the end of the study. For the list for school age children, there is a parent version of the form, that lists letters next to each experience, and a staff version of the form which lists the corresponding code associated with each letter that the staff member should indicate on the data extraction form. For the experiences whose corresponding code begin with "CE0", staff should first use one of the "other events" codes and then indicate the corresponding "CE0" code in the "other events" section of the data extraction form. Ask if the child has had any of the experiences on the list since the previous visit. Follow the instructions above for Parent Life Experiences. If the child has experienced something not listed, specify the event, write 32, the number for child other event, in the table above and ask about the impact of the event (if applicable 33 should be used for a second child other event; 39-43 are also available for use if the parent reports more than two "other events").

3. Beginning at the 10 year visit, give the child the card with a list of Child Life Experiences entitled "Experiences of Children when they are 10 years old". The administration of the Child Life Events (CLE) list will be very similar to the parent-completed LE list and will be given at every visit beginning at age 10 (i.e., twice a year for autoantibody negative families, four times a year for children who have been deemed persistent autoantibody positive). In clinic, a two-page CLE list will be given to the child to review. A cover sheet giving short, clear instructions for the CLE interview process should be stapled on top. Children will be instructed to carefully read over the list and circle any events that have occurred since their last TEDDY visit. Staff will then ask the child to state the events they have circled or to state the corresponding letter. There is a child version of the CLE that lists letters next to each experience, and a staff version of the form which lists the corresponding code associated with each letter that the staff member should indicate on the data extraction form. Staff will then follow-up with a question about the impact of the event. Children should complete the CLE list without input from their parent. If the child reports an event listed, write the number of the event, child's age (in years and months) – there is a check box on the online form for "Date of event not provided by child" for situations in which the child does not provide the date and impact on child. Then ask if something else has happened to him/her that is not on the list but he/she considers important and had an impact on him/her. For the experiences whose corresponding code begin with "CE0", staff should first use one of the "other events" codes and then indicate the corresponding "CE0" code in the "other events" section of the data extraction form. If the child has experienced something not listed, specify the event, write 58, the number for child other event, in the table above and ask about the impact of the event (if applicable 59 should be used for a second child other event; 60-64 are also available for use if the child reports more than two "other events"). If the child reports that an event is continuous, document the age of the child (in years and months) when the event first began and then mark the continuous life event field. Also see MOO section 10 for more information on the "Child-Report Questionnaires".

"Experiences of Children when they are 10 years old" Questionnaire for Long Distance Protocol (LDP) subjects

1. The questionnaire should be used only for LDP children.
2. The questionnaire should only be mailed or emailed. At this time, we are not adding this questionnaire to the portal (due to the chance of non-LDP families completing it).
3. Parents and children should be instructed that the Child Life Events Questionnaire is to be completed independently by the child. Staff should not disclose child-reported life event data to the parents – this information is confidential.
4. There are two versions of the questionnaire. The "Life Events Questionnnaire_LDP_3 mon" should be used for children who are on the 3 month visit schedule. The "Life Events Questionnnaire_LDP_6 mon" should be used for children who are on the 6 month visit schedule. The appropriate form should be used based on the child's assigned visit schedule, which is based on their autoantibody positive status, not their actual visit timing. For example, even if an autoantibody positive child is completing visits less often than every 3 months, they should still be given the questionnaire for a 3 month time frame.
5. Only data provided by the child on the Life Events Questionnaire should be recorded on the data extraction form. For example, if a parent reports that an event occurred in July 2017, do not extrapolate this event date to the child questionnaire/data extraction form. Similarly, do not inquire with parents about the date of an event reported by the child – child-reported data is confidential.
6. If a child leaves the date of an event blank on the questionnaire, no age of child will be added to the data extraction form; staff member should mark check box for "Date of event not provided by child".
7. Do not designate "continuous" for events reported on this form. The "continuous" check box should be left blank on the data extraction form. (Note: In-clinic administration will remain unchanged and "continuous" should be coded when appropriate)

Tips for recording Life Experiences

- If a parent-reported life event affects both a parent and a child, it is important to record it only once i.e. either as a mother (parent) life experience or as a child life experience on the parent-reported section of the TEDDY book extraction form (tables under question #10a and #10b). For example if the family has moved – #16 - (the child included) the event can preferably be reported as a parent life experience. Another example: if the child has been hospitalized report #24 as a child life experience and not #4 "a family member was hospitalized". However at the 10 year visit and on (once the child starts to also report life events), if both parent and child report an event independently, it should be recorded once on the parent-reported section of the TEDDY book extraction form (tables under question #10a and #10b) and once on the child-reported section of the TEDDY book extraction form (tables under question #10c).
- If there is a question about whether a parent-reported event should be listed as a parent or child life experience, the decision should be based on who the event affects the most.
- Always be sure to indicate the age of the child when the event occurred.

- Always be sure to mark the impact on both the child and the parent for events reported by the parent (tables under question #10a and #10b); at the 10 year visit and on for events reported by the child, only the impact on the child should be indicated (tables under question #10c). If there was no impact on the child or parent, "none" should be entered as the impact.
- If you do not have a record of the impact information, you should obtain it by asking at the child's next visit or, if you prefer, by calling the parent.
- Life events can be acute or "continuous." Acute life events are things that occur once within a relatively short time frame. Continuous life events are those that reoccur over a substantial amount of time, defined as ≥ 1 month. For example, "serious arguments/conflict with spouse/significant other" could be an acute stress occurring on one occasion during the interview period. Or it could be a continuous stress if it occurred repeatedly over ≥1 month interval. On the three month interview, check "continuous" if the life event is an ongoing stress at the time of the interview or lasted ≥ 1 month during pregnancy or since the birth of the child. Be sure to indicate the age of the child at the time the stress first occurred if it occurred since the birth of the child. For all subsequent visits, "continuous" should be checked whenever a life event is ongoing at the time of the interview or lasted ≥ 1 month during the time since the last study visit.
- If an event is listed as continuous, the age of the child, when the event first occurred, should be entered on **each** TEDDY Book extraction form.
- For continuous life events, the impact (on both parent and child for events reported by the parent (tables under question #10a and #10b); at the 10 year visit and on for events reported by the child, only the impact on the child should be indicated (tables under question #10c) must be recorded on **each** TEDDY Book extraction form.
- If the parent or child (at visits beyond the 10 year visit) does not mention a continuous life event at the next visit, the event should not be indicated on the new extraction form. If the parent or child (at visits beyond the 10 year visit) does mention the continuous life event again, then it continues to be a continuous life event and all information should be recorded (including the impact on both parent and child for events reported by the parent (tables under question #10a and #10b); at the 10 year visit and on for events reported by the child only the impact on the child should be indicated (tables under question #10c)). Ideally, if you happen to notice a continuous event was coded last time and the parent does not mention it this time, you may wish to prompt them for the information.
- If the parent or child (at visits beyond the 10 year visit) indicates that a continuous life event which has been recorded as a continuous life event on a previous extraction form(s) has ended, then nothing needs to be recorded on the new extraction form.

11.3.3 After the clinic visit

When the clinic visit is completed, all data requiring a DCC specified code should be coded (see MOO section 17.2.4. for instructions). Make sure the Extraction Form is filled in properly.

Follow the instructions in section 17.2.5 – 17.2.7 on how to scan the Extraction Form, upload and transfer the information to the DCC or you can enter the data directly online through the Enter/Edit/View page (see section 17.1.2).

11.4 TEDDY Calendar and TEDDY Notes Booklet

At the 6 year visit, the parent or primary caretaker will be introduced to the TEDDY Calendar (Note: in January 2012 the Finnish site decided to use the TEDDY Book data collection format again for all of its subjects, instead of the calendar data collection format).

In January 2014 all sites began using the TEDDY Notes Booklet, which is a condensed version of the annual TEDDY calendar, for children 6 years old and older. The TEDDY Notes Booklet does not use stickers, but has an annual calendar on the first page and the same category sections (dietary supplements, medications, vaccinations, etc) for parents to write down information to be extracted at the next visit by the TEDDY staff.

This is a calendar that is to be used by the parent to record events in their child's life that are of interest to the study. Parents are instructed to write down things such as use of dietary supplements, medications, vaccinations, height and weight history of the child, illnesses and symptoms of the child, doctor's visits and hospitalizations, school and social group interactions, and life events of the child. Stickers are provided to help the parent record events with the most accurate detail. The parent will be asked to bring in the TEDDY calendar to each clinic visit. (See below for detailed instructions.)

At each visit study personnel will go over the TEDDY calendar with the parent or primary caretaker and extract pertinent information using standardized study forms. It is not mandatory for the child's parent to use the TEDDY calendar, but the parent should be encouraged to use the calendar to record what happens to the child between clinic visits. The aim of the calendar is to make it easier for the parent to recall what has happened to the child between the clinic visits and to help improve efficiency of each study visit. The TEDDY calendar might also serve as a contact- and rapport-building tool between parents and TEDDY personnel.

11.4.1 Introduction of the TEDDY Calendar

At the 6 year study visit give the calendar to the parent or primary caretaker and fill in the child's name and the local study contact phone number.
Explain the purpose and use of the TEDDY calendar including:

- The aim of the calendar is to help the parent remember what happens to the child between study visits,
- Explain that stickers are provided to assist the parent in recording important dates and details. Explain that sticker use is optional.
- The TEDDY calendar works best if it is filled in frequently – for example once a week or every second week,
- Filling in the TEDDY calendar will make the study visits shorter, and
- Parents will be allowed to keep each annual calendar once the child has reached the age of the next calendar.

Read the letter to the parent and child and help the child find their TEDDY site on the world map. Show the parent and child the kid stickers they can use on the calendar pages. Show the parent and child the visit sticker page where

they can collect a different sticker each time they bring their calendar to a TEDDY visit.

11.4.2 Instructions on how to fill in the TEDDY Calendar

Study staff should show each section of the calendar and explain the purpose of each section to the mother. Specify how to use the stickers and the notes section on the calendar page corresponding to the current visit. Encourage parents to refer to the instructions pages in the back as needed. On the summary page, record events that are ongoing including chronic diseases, medications, supplements, school and social groups, and the status of vaccinations.

Study staff should refer back to the TEDDY book instructions as needed for specific guidance involving data collection in content areas that continue in the older child. The parent instructions for use of the calendar are included below:

- **Use the Allergy Sticker** to record new allergies to dust, animals, food, etc. Note the type of allergy and circle whether it is diagnosed by you or your **Healthcare Provider (HCP)**. Place the sticker on the calendar date when an allergy starts. Record any allergy symptoms and if the allergy was diagnosed by skin test, blood test, challenge test, other clinical test, no clinical test was done, or do not know whether test was done in the notes section on the opposite page of the calendar. Use a stop sticker if an allergy stops.

- **Use the Dietary Supplement Sticker** to record new dietary supplements such as single vitamins, multivitamins, probiotics, fish oils, antioxidants, etc. We would like to know the type of product, the brand name, the dose and number of times given weekly. Place the sticker on the date a supplement starts. Write any additional details in the notes section on the opposite page of the calendar. Use a stop sticker if a dietary supplement stops.

- **Use the Doctor Visit Sticker** to record when your child goes to the doctor and also the name of any medications your child has been given by the doctor. Place the sticker on the calendar date of the visit or on the date a medication was started. Write the reason for the medication, the total number of days it was given, and any additional details in the notes section on the opposite page of the calendar. Use a stop sticker if an ongoing medication stops.

- **Use the Hospital Visit Sticker** to record when your child goes to the hospital or urgent care facility. Place the sticker on the calendar date it happened. Include the name of the hospital and the reason for the visit. Write the number of nights your child was hospitalized and any other additional details in the notes section on the opposite page of the calendar.

- **Use the Illness Sticker** to tell us when your child is sick including any symptoms and/or presence of fever. Write yes if there is fever equal to or higher than 101° F or 38°C, and circle if the illness is diagnosed by you or

your **HCP**. Place the sticker on the date the illness starts. If the child had a fever, write whether or not it was measured and any other additional details in the notes section on the opposite page of the calendar. Use a stop sticker to tell when an illness stops.

- **Use the Life Events Sticker** to record new events you consider important in your child's life as well as events that affect the family as a whole. Place the sticker on the calendar date to note your child's age at the time the event occurred. Please record the effect it had on you and also on your child using either Good, Bad, Very Bad, or None. Write any additional details in the notes section on the opposite page of the calendar.

- **Use the Other Medication Sticker** to record the names of any other over-the-counter medication your child has been given. Write the reason for the medication, the total number of days it was given, and any additional details in the notes section on the opposite page of the calendar. Use a stop sticker if an ongoing medication stops.

- **Use the School and Other Activity Group Sticker** to record the month when your child begins school or changes a grade level or activity group. Activities that occur outside of school could be organized sports teams (baseball, soccer), group lessons (dance, karate, band) or after-school activities (art, sports, music, after-school care) or social development groups (boy or girl scouts, 4-H club). We are interested in those activities that your child is regularly participating in at least once a week or more, for at least one month that include being around other children. Please include the number of hours they attend school or the other activity group per week. Write any additional details in the notes section on the opposite page of the calendar. Use a stop sticker if school or a group stops.

- **Use the Special Diets Sticker** to record if your child is on a special diet for any reason. If your child follows a vegetarian diet, please tell us what types of food your child eats on this diet. Circle whether the new diet is recommended by you or your **HCP**. Place the sticker on the date a diet starts. Write any additional details in the notes section on the opposite page of the calendar. Use a stop sticker if a diet stops.

- **Record Vaccinations in the notes section** that can be found on the opposite page of the calendar. You may also bring a copy of your child's vaccination record to the visit.

- **Record Weights and Heights in table on page 40.**

- **Use the Things to Know Sticker** to record anything else you think is important for us to know. Place the sticker on the corresponding calendar date. Write any additional details in the notes section on the opposite page of the calendar.

Reminder Stickers
Note: Study staff may want to remove and retain these stickers since they will mostly be used by study staff and not the parents.

> **TEDDY Visits:** During each visit, study staff should place an appointment reminder sticker on the corresponding calendar date for the next scheduled TEDDY visit.
>
> **Three Day Food Record:** During each visit, study staff should suggest three ideal diet record days for the next study visit and place the diet record reminder stickers on those corresponding calendar dates.
>
> **Poop Sample Collection:** During each visit, study staff should place stool sample reminder sticker(s) on the ideal date(s) suggested for the collection of the next stool sample(s).
>
> **Water Sample Collection:** During the bi-annual visit, study staff should place a water reminder sticker on the ideal date suggested for obtaining a water sample if one is expected at the next visit according to the study protocol.

After the TEDDY calendar has been reviewed in detail, remind the parent of the advantages of keeping the TEDDY calendar up to date. However, tell parents that they do not HAVE to fill in the calendar (i.e., it is not a requirement of the study), but that it is better to record some things than nothing.

FAQs for entering data on the 6-15 year extraction form:

Q: I see that the date of 1st,2nd, 3rd, 4th and 5th vaccine has been replaced with just date of vaccine. Does the data field in which a vaccine is documented matter?

> **A**: The data field the vaccine is documented does not matter, for analyses the dates will be automatically put in chronological order.

Q: For the SC codes for level or grade of school, should we request new codes or will the DCC be making codes based on a specific range?

> **A**: Sites should request codes when they need them as the levels/grades will vary by country.

Q: Do we need to "close out" the school code DC003: Group Daycare Institution (church daycare, employer daycare, all day/ full-time pre-school, pre-k, kindergarten, private company) under the Daycare question when we document a new SC code for 1st grade?

> **A**: Yes, you should close out the DC003 code when the subject starts 1st grade – if this information is obtained at the 6 year visit or before, the close out should be indicated on the 2-5 year Data Extraction Form daycare question; if the information is obtained at the 6 year 3 month visit or after, the close out should be indicated on the 6-15 year Data Extraction Form school question.

NOTE: The Psychosocial Committee did not want to collect "Total # of children" for school or other social groups on the 6-15 year Data Extraction Form, so sites will not enter this information when they are closing out the code on the 6-15 year form.

Q: How should we indicate first grade on the TEDDY Book 2-5 year extraction form if the child starts first grade while this extraction form is still being administered?

A: The constraint for question #10 (Daycare) on the TEDDY Book 2-5 year Data Extraction Form has been changed so that the type of daycare code field now allows sites to enter SC codes (Level or grade of school codes) in addition to the SG and DC codes.

Q: What should be indicated as the until date for a grade level when the child does NOT attend summer school?

A: The until date for that grade should be the start of the summer break.

(NOTE: the system will not let you enter future dates, so you will have to wait to enter the until date until after the date has passed.)

Q: What should be indicated as the until date for a grade level when the child DOES attend summer school?

A: The until date for that grade should be the end of the summer school date.

(NOTE: the system will not let you enter future dates, so you will have to wait to enter the until date until after the date has passed.)

Q: Does a stop date need to be entered for school or an activity group for a short break?

A: Lapses in day care/social group/school attendance of greater than or equal to 1 month need to be indicated on the TEDDY Book extraction form. Thus if the child does not attend the day care or social group or school for periods of time less than 1 month, the lapse in attendance does not need to be recorded.

Q: We have a child who is 6 1/2 years old. He is currently in kindergarten, recorded as DC003 on 2-5 year extraction form in the daycare section. For the 6 year 3 month visit the question asks "Has the child been enrolled in school or had a change in grade level since the last report?" What answer, "YES" or "NO", should we mark? How should we answer the question "In the last 30 days, what was the means of transportation that your child used on most days to get to school?"

A: "NO" should be marked since the child has not been enrolled in a new grade. Site should answer the transportation question accurately by choosing either active transportation or passive transportation.

Q: We need clarification on coding School and Other Activity Groups.

A: From Data Extraction Form:

School or Other Activity Groups
As in the past with day care and social groups, we now would like to know more about the time your child spends in school, in after-school activities and in regular recreational activities. Below is a place to record school situations and the next page is for other activity groups.

Other Activity Groups: *Activities that occur outside of school could be organized sports teams (baseball, soccer), group lessons (dance, karate, band) or after-school activities (art, sports, music, after-school care) or social development groups (boy or girl scouts, 4-H club). We are interested in those activities that your child is regularly participating in at least once a week or more, for at least one month that include being around other children. Does the child regularly participate (at least once per week, for at least one month) in activities such as sports teams, group lessons, organized after-school programs or social groups or has there been a change in these activities since the last visit?*

General Instructions:

- Before or after school situations are (even ones that are at school) should be recorded as social group activities.
- Daycare codes are being phased-out of use for those older than 6 years old (7 and over) and social group codes should be used depending upon the circumstances.
- School situations are those that have normally been coded by grade level, including extended school hours of being in-school should continue to be coded with school codes.
- School codes should not be used to code group activities.
- Other Activity Groups ages 12-15 should include regular activities (once a week or more) where the child is around other adults and/or children not part of the child's immediate family. This would include time volunteering and/or working. Coding for these will follow the same rules as other activity groups based on activity focus.

Key elements and probes for accurate coding:

- The key elements that we are trying to capture here are:
    - Probe: Does this activity entail being in a GROUP of children? Size of group not being assessed. This is more than going to the babysitter or a relative's house.
        - After school care in a group situation at school or elsewhere should be coded as SG024 or SG025, depending upon the level of activity.
    - Probe: Does this group include a physically active component/purpose? Distinguish between a group that includes a more physically active component (sports teams, lessons that are active, e.g. dance, karate), Vs one that is less active (music lessons, chess club, study hall, after school care in home that isn't active, boy/girl scouts)
        - For some groups the physical activity will be the main purpose
        - For others there could be mixed activities that include some physical activity and some less non-physically active purpose. For those when OVER 50% of time is spent physically active

or where main purpose is about a sport or being physically active, then it should be coded as SG024.

- For all groups, regularity is important distinguishing factor-at least 1 time per week for at least 1 month.
- Summer Camps: Use the above distinctions to assess whether this should be coded as SG024 or SG025.
- Summer School: Code using school codes

Q: We need clarification on camp question:

Q1) Day camp has started and finished at the time of the TEDDY interview:
A1) Document the month/year for start and end, the type of camp and appropriate SG code. Document the TOTAL # of days attended and the hours/day.

Q2) Overnight camp has started and finished at the time of the TEDDY interview:
A2) Document the month/year for start and end, the type of camp and appropriate SG code. Document the TOTAL # of days attended and select overnight camp.

Q3) Day camp has started but is ongoing at the time of the TEDDY interview:
A3) Document the month/year for start, leave the end blank (we cannot document dates for the future), the type of camp and appropriate SG code. LEAVE THE TOTAL # of days attended BLANK (we won't know until the camp is done). Document the hours/day attended.

Q4) Overnight has started and is ongoing:
A4) Document the month/year for start, leave the end blank (we cannot document dates for the future), the type of camp and appropriate SG code. LEAVE THE TOTAL # of days attended BLANK (we won't know until the camp is done). Select overnight camp.

Q5) At a future visit, the day camp has now ended, do the same as #1:
A5) Document the month/year for start and end, the type of camp and appropriate SG code. Document the TOTAL # of days attended and the hours/day.

Q6) At a future visit, the overnight camp has now ended, do the same as #2:
A6) Document the month/year for start and end, the type of camp and appropriate SG code. Document the TOTAL # of days attended and select overnight camp.

Q. How to document age of an event based on the birthday when the parent/child doesn't know the exact date? An age calculator is used by some clinicians when the exact date of an event is known: https://www.calculator.net/age-calculator.html; when only the month is known, is an estimate okay?

A. If the family can identify the month, ask if they know beginning, middle or end of the month. Beginning: Use the 1st of the month. Middle: Use the 15th. End: Use the 30th of the month. If family is unsure of when in the month, use

the middle – the 15th. Figure child‘s age from that date for the extraction form.

12. TEDDY Diet Study

NOTE: In August 2018, the collection protocol was changed so as to continue to collect 3 day diet records every 6 months from subjects who are single or multiple persistent confirmed autoantibody positive (even if the subject reverts to autoantibody negativity) and to stop 3 day diet record collections on all other subjects after the 10 year visit. Should a subject be deemed single or multiple persistent confirmed autoantibody positive after the 10 year visit, the 3 day diet record collection will be restarted at the next visit. This will provide a complete dataset on all subjects up through 10 years of age and continued collection on persistent confirmed autoantibody positive subjects through the end of the study. Continued data collection on persistent confirmed autoantibody positive individuals will enable the TEDDY study to explore the role of diet, and dietary changes, through early adolescent years, on progression to T1D. It has been noted that the diet of individuals in this 10-15 year age interval is changed as compared to the diet at younger ages. These data will enable TEDDY to include these dietary patterns in assessments of T1D risk along with other exposures and changes occurring during the peri-pubertal period to include energy intake, energy expenditure, growth, hormonal changes and glucose demand. Epidemiological data points to increased T1D incidence during this period, TEDDY has also observed a declining rate of conversion from autoantibody negative to autoantibody positive (i.e., lower incidence of seroconversion during this age range). This reduces the statistical power to see an effect of dietary changes during the 10-15 year age range. Coupled with a lower compliance rate, as compared to families completing the 3 day diet record whose child is persistent confirmed autoantibody positive, it seems prudent to reduce the burden on families and clinic staff by discontinuing data collection after 10 years of age for families whose child is autoantibody negative. TEDDY will have a complete data set on this population through age 10 years so it will be able to address the contribution of diet in the cumulative incidence of islet cell autoimmunity up to this age.

NOTE: In 2020, it was decided that ALL 3 day diet record collections on ALL subjects would stop April 1, 2020.

12.1 Rationale

The goals of the dietary collection component of TEDDY are 1) to identify dietary factors that predispose to or protect from islet autoimmunity and T1DM; and 2) to identify potential differences in dietary determinants of islet autoimmunity and T1DM across diverse populations and ethnic groups.

TEDDY is designed to test and confirm existing dietary hypotheses as well as explore new, less well-documented hypotheses. Examples of the former include the association of persistent islet autoimmunity with:

- early and late exposure to cereals or gluten in the infant diet
- short duration of breast-feeding
- exposure to cow milk in infancy and later in childhood

- lower intake of vitamin D or omega-3 fatty acids.

Examples of the latter include animal data and limited human data supporting the association of persistent islet autoimmunity with:

- lower intake of vitamin E (α-tocopherol) alone, or in combination with certain other antioxidants
- lower intake of zinc via the water supply
- higher intake of nitrites via the water supply.

Studies from DAISY and BabyDiab investigators recently suggested a strong association between timing of first exposure to cereals and risk of islet autoimmunity (Ziegler et al, 2003; Norris et al, 2003). These two studies, while remarkably consistent, did not agree on whether the exposure in question was to all cereals or to only gluten-containing cereals; and whether late first exposure (after 6 months) increased risk of islet autoimmunity in addition to early exposure.

In order to investigate this issue further and resolve these discrepancies across studies, it is necessary to use common data collection protocols, the same recruitment criteria and the same follow-up protocols. Questions remain as to whether this association is driven by dose or quantity of exposure, or whether it is related to a proportional measure, such as percent energy from carbohydrates. In order to quantify exposure, one needs to collect information on the entire diet, which would allow one to get absolute intake (as opposed to frequency) and to adjust for energy intake. This requires the collection of a food record. There are no adequate biomarkers to measure the intake of cereals or specifically gluten. The findings of both case-control and cohort studies are inconsistent regarding the putative effects of cow milk intake on beta-cell autoimmunity and T1D (reviewed in Virtanen and Knip 2003).

One prospective cohort study and a retrospective case-control study have reported a reduced risk of T1D after vitamin D supplementation in infancy (Hypponen et al 2001, EURODIAB 1999). A case-control study suggested that cases of T1D were less likely to have been given cod liver oil, which contains, in addition to vitamin D, vitamin A and the omega-3 fatty acids, DHA and EPA, in infancy compared with controls (Stene et al 2003). The next step in investigating the role of vitamin D (Norris et al, 2001) and fish oil is to use a prospective study design with complete dietary assessment and biomarkers. Therefore, in addition to the previously mentioned food records, TEDDY will measure the biomarkers, 25,hydroxyvitamin D and erythrocyte membrane fatty acid composition in blood samples drawn from study subjects.

TEDDY also proposes to study more exploratory hypotheses. High dietary intake of the anti-oxidant, vitamin E, have been shown to delay or prevent the onset of diabetes in NOD mice (Hayward et al, 1992) and BB rats (Murthy et al, 1992, Behrens et al, 1986). In a nested case-control study higher serum alpha-tocopherol levels were related to lower risk of T1D in adults (Knekt et al. 1999). Serum alpha-tocopherol is a measure of anti-oxidant status in individuals. We hypothesize that low levels of alpha-tocopherol is associated with the development of islet autoimmunity. Other anti-oxidants, such as the carotenoids, ascorbic acid and selenium could work independently or in concert with alpha-tocopherol in preventing or reversing islet autoimmunity. Therefore, in order to investigate these exploratory hypotheses, we will collect intake of these micronutrients via the diet records as

well as measure plasma levels of alpha-tocopherol, the carotenoids, and ascorbic acid. We will measure the anti-oxidant, selenium, via toe nail clippings in order to preserve the blood samples for other biomarkers that can only be measured in the blood.

Haglund et al (1996), Zhao et al (2001) and Stene et al (2002) suggested that zinc concentration in water was inversely associated with diabetes risk. Kostraba et al (1992) and Parslow et al (1997) suggested that higher nitrate concentrations in the water were associated with diabetes risk. And Stene et al (2002) suggested that a lower pH level of drinking water is associated with increased diabetes risk. We will investigate these hypotheses in TEDDY by collecting a sample of tap water, which will be tested for zinc, pH and nitrate.

References

Behrens WA, Scott FW, Madere R, Trick K, Hanna K. Effect of dietary vitamin E on the vitamin E status in the BB rat during development and after the onset of diabetes. Ann Nutr Metab 1986;30:157-65.

EURODIAB Substudy 2 Study Group. Vitamin D supplement in early childhood and risk for type 1 (insulin-dependent) diabetes mellitus. Diabetologia 1999;42:51-4.

Haglund B, Ryckenberg K, Selinus O, Dahlquist G. Evidence of a relationship between childhood-onset type 1 diabetes and low groundwater concentration of zinc. Diabetes Care 1996;19:873-5.

Hayward AR, Shriber M, Sokol R. Vitamin E supplementation reduces the incidence of diabetes but not insulitis in NOD mice. J Lab Clin Med 1992;119:503-7.

Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet 2001; 358:1500-3.

Knekt P, Reunanen A, Marniemi J, Leino A, Aromaa A. Low vitamin E status is a potential risk factor for insulin-dependent diabetes mellitus. J Intern Med 1999;245:99-102.

Kostraba JN, Gay EC, Rewers M, Hamman RF. Nitrate levels in community drinking waters and risk of IDDM. An ecological analysis. Diabetes Care 1992;15:1505-8.

Murthy VK, Shipp JC, Hanson C, Shipp DM. Delayed onset and decreased incidence of diabetes in BB rats fed free radical scavengers. Diabetes Res Clin Pract 1992;18:11-16.

Norris JM. Can the sunshine vitamin shed light on type 1 diabetes? (Invited Commentary) Lancet 2001;358:1476-8.

Norris JM, Barriga K, Klingensmith G, Hoffman M, Eisenbarth GS, Erlich H, Rewers M. Timing of Cereal exposure in infancy affects risk of islet autoimmunity. The Diabetes Autoimmunity Study in the Young. JAMA 2003; 290:1713-20.

Parslow RC, McKinney PA, Law GR, Staines A, Williams R, Bodansky HJ. Incidence of childhood diabetes mellitus in Yorkshire, northern England, is associated with nitrate in drinking water: an ecological analysis. Diabetologia 1997; 40:550-56.

Stene LC, Joner G, Norwegian Childhood Diabetes Study Group. Use of cod liver oil during the first year of life is associated with lower risk of childhood-onset type 1 diabetes: a large, population-based, case-control study. Am J Clin Nutr 2003;78:1128-34.

Stene LC, Hongve D, Magnus P, Ronningen KS, Joner G. Acidic drinking water and risk of childhood-onset type 1 diabetes. Diabetes Care 2002;25:1534-38.

Virtanen SM, Knip M. Nutritional risk predictors of □ □cell autoimmunity and type 1 diabetes at a young age. American Journal of Clinical Nutrition 2003;78:1053-67.

Zhao HX, Mold MD, Stenhouse EA, Bird SC, Wright DE, Demaine AG, Millward BA. Drinking water composition and childhood-onset type 1 diabetes mellitus in Devon and Cornwall, England. Diabet Med 2001; 18:709-17.

Ziegler A-G, Schmid S, Huber D, Hummel M, Bonifacio E. Early infant feeding and risk of developing type 1 diabetes-associated autoantibodies. JAMA 2003; 290:1721-28.

12.2 Training and Certification for Collection of the TEDDY 24-hour Recall and Food Records

Throughout the TEDDY protocol, individuals responsible for collecting dietary information will be seen by study nurses/dietary interviewers/nutritionists to reflect the different types of research staff conducting the study at different sites. Regardless of other qualifications, only those individuals who have received TEDDY-approved training and certification in the collection of the 24-hour recall and the 3-day food record will be eligible to collect dietary data. The training and certification procedures are described below.

Each site will designate a lead nutrition person who oversees the collection and local quality assurance of the 24-hour dietary recall and the 3-day food records. At the Swedish and Finnish sites, study nurses are responsible for administering the 24-hour recall and the 3-day food record. The lead nutritionist for Finland is located in Helsinki or Tampere; the lead nutritionist for Sweden is located at Malmö.

At the German site, research-trained personnel, mainly nutritionists are responsible for administering the 24-hour dietary recall, and collecting the 3-day food record from the TEDDY families and the data extraction of the TEDDY book. Germany has two lead nutritionists, one in Munich who oversees the data extraction and coding and one in Dortmund checking the completeness of food records and overseeing the data entry and processing of data.

At the US sites, the dietary interviewers are research-trained personnel, of whom some but not all are nurses or nutritionists. Those lead nutrition persons who are not Registered Dieticians and/or trained Nutritionists may need to consult with qualified nutrition personnel for resolution of dietary questions as needed. The nutritionist at the DCC will serve in this advisory role for all TEDDY sites as needed, and will also oversee collection and quality assurance of dietary data.

12.3 General Training of Research Personnel

All TEDDY staff members engaged in data collection must be trained and practiced in the cross-disciplinary elements common to the TEDDY protocol to be certified to engage in study activities. The cross-disciplinary elements of the training are the same for the life of the study and include:

- Successful completion of Humans Subjects Protections Training course.
- Successful completion of the centralized training or review of video tapes and presentations under the direction of a certified trainer.
- Reading the Manual of Operations and the Protocol related to all visits.
- Training and testing of coding accuracy to ensure cross-site comparability of coding.

Nutrition Field Personnel Groups

Field personnel are defined as study nurses and physicians (in Sweden and Finland), dietary interviewers (in US and Germany) and nutritionists (in Germany) who are responsible for collecting data in the field. A site lead nutrition person is either a nutritionist or a person trained in coding and quality control who is located at each site and is responsible for food coding, data entry and quality control. To achieve standardization and accuracy of the

research interview, nurses/dietary interviewers/nutritionists and site lead nutrition persons must fully understand the TEDDY protocol and their individual responsibilities for the study.

Specialized Training Overview

Dietary field personnel receive the same training as other clinical staff, but in addition they require more precise information about baby foods and food supply in general. Examples include estimation of portion sizes, various means of measuring consumption (e.g. household measures, picture booklets, brochures of industrial foods and weight lists of different sized food items), and data coding of foods. Field personnel (in Finland – nutritionists) must know the classifications of foods in the country-specific food database, selection of foods and supplements, and codes that can be used in the food data entry and modifications or simulations of recipes. In addition, topic such as yields after preparation, recipe models, cookbooks, and nutrient composition tables, dilution ratios etc. are important aspects of training. Field personnel must also acquire interview skills and database skills that are specific to the TEDDY diet study.

At the end of successful trainings field personnel and site lead nutrition persons receive certificates. Details of the training are provided in the sections below.

Interview Training

Field personnel are trained to carry out 24-h recalls, check food records, understand the variety of products and supplements in the country in question, estimate portion sizes and comprehend the general characteristics of database in use and the possibilities it offers. The research method and its strengths and weaknesses, ways of estimating portion sizes and the guiding questionnaire are discussed in training of 24-h recalls.

In addition, field personnel are given a demonstration of a 24-h recall. A videotaped presentation demonstrating the recall interview and techniques has been prepared in English and is available on the TEDDY Web site. It is mandatory for new English-speaking interviewers who enter the study to view this tape. TEDDY sites in Europe have developed face-to-face training that new personnel entering the study must follow.

The sequence and style of questioning during dietary interviews can have a major impact on patient responses and thus on overall data validity and reliability. It is of paramount importance that the food record method and its characteristics (including giving the recording dates beforehand and acting neutral in the situation of checking the food records) are discussed in training. Other areas of importance in training include:

- Emphasis on the important stages of food record verification: first check the timing of meals, then amounts eaten and finally the details of the meal (i.e. preparation, processing, ingredients used, quality of the ingredients, etc.)
- Instruction to probe for specific ingredients in foods. An ordinary recipe (examples: chicken soup, beef gravy, tomato sauce, meatloaf) does not specify exactly what kind of a meal is in question and requires a detailed list of ingredients used and their qualities.
- Instruction to probe for qualities of liquids, milks, cheeses, cold cuts, meats, fish, cereals, milk products etc., as well as possible omissions of foods used together, sugar and salt added, snacks and small portions given to the child for tasting.

- Instructions in the tools and methods to estimate portion sizes, including use of the graphics that have been prepared for TEDDY families to help them make accurate food records.
- Instructions to probe for dietary supplements, and "fortified" foods with added nutrients (such as calcium-fortified orange juice or 100% RDA-fortified "Total" breakfast cereals).
- Training of database and software in use and rules for data entry (e.g. simulation of recipes and possible modifications of recipes), and understanding how the use of software impacts the interview process.
- Relationships among the food records and other data collected, such as data entered into the TEDDY Book, family questionnaires and non-dietary interviews.

In training of the field personnel examples of perfectly and not so perfectly filled out food records can be used for teaching accuracy and thoroughness.

Site-Specific Certification & Training: Finland, Sweden, Germany

The certificate of field personnel is granted after three successfully done 24-h recall exercises and two real cases and three successfully done 3-day food record exercises and two real cases.

CERTIFICATE FOR 24-HOUR RECALL & FOOD RECORD FOR RESEARCH NURSES/DOCTORS

1. Three 24-hour recall exercise cases acceptably and two real ones acceptably
2. Three 3-day food record exercise cases acceptably and two real ones acceptably
3. Four to six annual training sessions (modify data collection strategies as needed in order to facilitate data collection age groups).

The certificate of nutritionists is granted after three successfully done 24-h recall exercises and two real cases and three successfully done 3-day food record exercises and two real cases (i.e. same as for field personnel). In addition, the nutritionists need to successfully complete three data entry exercises and one test case and commit to participate continuously in discussions about topics in nutrition and data entry.

CERTIFICATE FOR 24 HOUR RECALL AND FOOD RECORD FOR NUTRITIONISTS

1. Same as for nurses and doctors
2. Three data entry exercises and one test case
3. Commitment to participate in regular discussion of nutrition topics & data entry.

Site-Specific Certification & Training: US TEDDY Sites

"Dietary interviewers" are defined as research personnel who have been trained and certified by the University of Minnesota Nutrition Coordinating Center (NCC) to use Nutrition Data System for Research (NDS-R) dietary data collection software to collect 24-hour dietary recalls and the food records from the participants. Dietary interviewers and lead nutrition persons attend a two-day training workshop at NCC to become familiar with NDS-R

program features, understand the NDS-R database structure, gain skill at data entry, editing and data management, increase or enhance their dietary interviewing skills and to learn their responsibilities for the TEDDY-specific dietary assessment protocol.

Consistent use of the multiple-pass approach, a TEDDY-specific introduction script and the TEDDY Food Visuals Booklet are required to promote standardization of the dietary recall collection. Prior to collecting TEDDY dietary records and recalls, all dietary interviewers will successfully complete NCC certification activities and be certified by NCC staff.

CERTIFICATE FOR 24 HOUR RECALL AND FOOD RECORD FOR DIETARY INTERVIEWERS

Upon successful completion of the following activities, the Nutrition Coordinating Center will notify the sites with the status of each dietary interviewer. Certification activities will include:

- Attendance at two-day training workshop
- Completion of a scripted baseline recall with NCC staff
- Collection of 10 unscripted recalls and food records from study-similar subjects (such as infants age 3-24 months) (5 recalls and 5 scripted food records provided by the NCC)
- Completion of a scripted follow-up recall with NCC staff

CERTIFICATE FOR 24 HOUR RECALL & FOOD RECORD FOR SITE LEAD NUTRITION PERSONS

Site lead nutrition persons must attend the two day training workshop and become certified. It is highly recommended that the site lead nutrition person observe both the 24-hour recall and the 3-day diet records for each of their dietary interviewers on a regular basis.

- Attendance at two-day training workshop
- Completion of a scripted baseline recall with NCC staff
- Collection of 10 unscripted recalls and food records from study-similar subjects (such as infants age 3-24 months) (5 recalls and 5 scripted food records provided by the NCC)
- Completion of a scripted follow-up recall with NCC staff
- Commitment to participate in regular discussion of nutrition topics and data entry

Site lead nutrition persons are responsible for ensuring the overall quality of the dietary data collected by the dietary interviewers in their charge. Specific procedures for checking the dietary data, observing interviews, documenting unusual foods and amounts and flagging unreliable recalls and records are provided at the training workshops and included in the "Dietary Data" section of the TEDDY Quality Control manual as well as in the "Quality Assurance Overview" section of this MOO chapter.

Continuing Education

The specialized training of field personnel in Finland, Sweden, Germany, and the US includes regular updates of news in nutrition and changes in food supply in their respective

countries. Updates (4 – 6 times per year) increase the knowledge of different food items and strengthen the reliability of data collection procedures. Field personnel must commit to participate in four to six annual training sessions concerning updating of knowledge and discussion of working with growing age groups as part of their ongoing certification.

Dietary interviewers at all sites are encouraged to review the TEDDY Manual of Operations throughout the project period in order to remain well versed on TEDDY specific protocol issues. The site lead nutrition person may hold refresher sessions periodically throughout the year to address problem areas and remind interviewers of the protocol.

Finland: Every clinic holds nutrition-related continuing education four times per year for study nurses. Activities include updates of newly launched commercial baby foods and infant formulas, reminder of easily forgotten issues when checking food records and TEDDY books, highlights of important coding issues, and discussing questions the nurses have faced when talking to the families. In addition, nutrition recommendations and important research findings are reviewed. Finnish nutritionists receive continuing education in the form of regular (once in a fortnight) conference calls. Topics include updates regarding vitamin and mineral supplements, food database coding issues, and recipes for industrial foods and new baby foods.

Germany: The lead nutritionists located in Dortmund oversees the market of baby foods (formula, gruels, jars) and informs the staff located in Munich immediately if new products especially formulas are available or if products are phased out. A picture booklet of formulas is updated continuously. Further more, all TEDDY staff members from Munich participate at a meeting once a week where current topics of interest such as coding decisions are reported and foreseeable questions/ problems are discussed.

Sweden: Group meetings are held with all study nurses 3 – 4 times per year. Discussions include difficulties and challenges in the food records the TEDDY books. Workshops with different themes are scheduled at least once per year.

A newsletter is sent out once a month to the study nurses. Letters cover new coding decisions, information of new baby foods products (and their content) and requests for attention on different diet related issues. Two times per term the lead nutritionist visits the TEDDY clinics outside the main clinic (situated in Malmö). The purpose of these visits is mainly to observe the study nurses when they interview a caretaker and give immediate feed backs. All study nurses should have at least one visit per year by the lead nutritionist. There are currently 11 study nurses employed at three different clinics.

US: The site coordinators or site lead dietitians inform dietary interviewers of decisions that impact daily data collection after diet committee conference calls and the NDS-specific conference calls. Periodical (e.g., bi-weekly or monthly) meetings with interviewers are to be scheduled at each site to communicate about food market changes, strategies facilitating data collection, updated documents posted on the TEDDY website, and other nutrition-related issues.

12.4 Data Collection Schedule

Three Month 24-Hour Food Recall

Prior to the 3 month visit the TEDDY First Questionnaire is mailed to the mother of the baby (or to the primary caretaker). The primary caretaker brings the completed questionnaire to the 3 month TEDDY visit, where the questionnaire is reviewed by the study nurse/dietary interviewer/nutritionist.

The 3-month visit takes place in the TEDDY research clinic for the Swedish, Finnish, and US sites. In Germany, families living outside of Munich are visited at the home of the family; families living in Munich attend the TEDDY research clinic. A 24-hour dietary recall is collected during the first TEDDY clinic visit which will take place when the TEDDY child is 3 to 4.5 months of age.

> **NOTE WELL:**
> Due to constraints in recruitment of TEDDY children, not all TEDDY 3-month visits will occur when the child is 3-months of age. The window for 3-month TEDDY visits extends until the child is 4.5 months of age. It is important for clinical staff to check and re-check the birth date of the child, as infant feeding practices can change considerably between 3 months and 4.5 months of age.

The purpose of the TEDDY 24-hour dietary recall is to obtain a record of the type and amount of foods, beverages, and vitamin/mineral preparations consumed by TEDDY infants during a complete 24-hour period preceding the interview. The interview "day" begins at midnight. Sites in the USA using the NDS-R Interview system are prompted by the computer screen to ask a question, such as "*What did the child have to eat after midnight*?"

Primary caretakers are not told in advance that they will be asked to give a 24-hour dietary recall at the 3-month visit. The 24-hour recall should be conducted after the 3-month interview takes place because the preceding interview regarding timing of introduction of foods and use of vitamin supplements might help the primary caretaker to recall the diet.

The study nurse/dietary interviewer/nutritionist carries out the 24-hr food recall using various visual aids to help subjects recall products and serving sizes. Each site has country-specific pictures of infant formula packages, baby food packages, and packaging for dietary supplements. The original bottles and jars are used in Germany when conducting the 24-hr recall at the participant's home. Sites could use one larger food atlas such as the UK Food Atlas as a backup reference in situations when the TEDDY Food Visuals Booklet is insufficient.

The TEDDY Food Visuals Booklet has been developed to help to ensure consistency in interviews and responses. The TEDDY Food Visuals Booklet contains:

- A Participant Copy of The Dietary Intervention Study in Children (DISC) Food Amounts Booklet (Metric version for European sites and English measurement version for US sites)
- Selected images of food drawings and portion size photographs from *Matmallen*, a booklet of food shapes from *Livsmedels Verket* Publishers, which is used with dietary research in Sweden

After the 24-hour recall is conducted, the nurse/dietary interviewer/nutritionist trains the primary caretaker on how to collect a 3-day food record.

Three month clinic visit: training primary caretakers on how to collect 3-day food records

The TEDDY Book, 3-day food record form (and the day care food record form if necessary) and the Food Visuals Booklet should be given to the mother (or to the Primary Caretaker) who will be trained to keep the food record. In Germany the families will be trained to weigh the foods. German families will be provided with a scale instead of the TEDDY Food Visuals Booklet.

The primary caretaker is instructed to collect the 3-day food record within one week of the clinic visit. When the next clinic visit date is scheduled, the mother is given the dates of three days (which include one weekend day and two weekdays) to complete the 3 day food record, allowing for enough time to finish it prior to the next clinic visit. Copies of the 3-day food record forms are attached in Appendix A.

NOTE WELL:

- While it is preferred that the three days of the food record be as close as possible to the birthday of the child to help ensure consistency of ages in the analysis of TEDDY food record data, take note that each 3 day diet record window is 6 weeks before and 6 weeks after the TEDDY participant's birthday up until 12 months of age, 6 weeks before and 12 weeks after the TEDDY participant's birthday at 12 months of age and is 12 weeks before and 12 weeks after the TEDDY participant's birthday beginning at 18 months of age through 15 years. The 3 day diet record for the particular clinic visit must be collected within the designated window.
- It is important to request that caretakers/parents bring to the clinic visit any wrappers, labels, boxes or other packaging from foods and supplements consumed during the 3-days recording period.

  It should be explained to parents/caretakers that there is a special pocket in the TEDDY book to hold labels and wrappers, and that having the food and supplement ingredients available and saved in these pockets will lend tremendous help to TEDDY researchers who are looking to find out if and how different foods and nutrients might be associated with T1DM. (In TEDDY German families, parents should be instructed to save the labels, etc., but will send them with the record to the clinic. Further information is obtained over the telephone.)

The dates of the 3-day food records do not have to be the three days exactly prior to the next clinic visit, but should be within 7-10 days of the visit, so that the primary caretaker may still be able to remember the days in question if the nurse/dietary interviewer/nutritionist needs to clarify something on the record. It is recommended that these days include two weekdays and one weekend day if at all possible.

Approximately 1-2 weeks prior to the next clinic visit, TEDDY mails the primary caretaker a packet which includes (among other things) the 3-day food record form and instructions (see Appendix A). The packet should include a reminder to the parents/caretaker to bring to the clinic visit any wrappers, labels, boxes or other packaging from foods and supplements that

are consumed during the 3-day recording period. The selected dates are to be written on the form – along with instructions indicating that if it is not possible to complete the food record during those dates, they can choose other dates on which they complete the food record. However those dates should include one weekend day and should be as close as possible to the child's next TEDDY visit. Some sites may choose to call the family 24 hours before their next clinic visit to remind them of the clinic visit and to bring in the completed food record when they come into clinic; other sites may choose to send reminder post cards/letters, emails, etc.

3-Day Food Record at the Six-Month through Twelve-Month Visits

For Finnish, Swedish, US, and German participants residing in Munich, these data are collected at each clinic visit from 6-months until 12-months. German participants, who live far away from Munich, will send the record with the labels to the clinic in Munich. Records are then sent to the FKE nutritionist in Dortmund who checks the diet records and phones the families to probe for missing information.

NOTE WELL:

- If a subject misses a TEDDY visit (thus a blood sample is not collected) or if a blood sample is unable to be collected at a TEDDY visit the 3 day diet record should still be collected.
- If the parent returns a 3-day diet record to the clinic staff with only one or two days completed, but is able to recall the dietary information for the missing day(s) and if the interviewer is confident in the quality of the data the parent is recalling, the diet record can be used. If the parent does not seem to be providing reliable data (guessing on amounts, etc.) then the parent should be thanked and reminded that for next time to write foods down soon after the baby eats and the diet record should not be submitted.

12.5 Data Collection Procedures

The 24-hour dietary recalls and the review of the 3-day food records are conducted in an in-person interview at the TEDDY study site during one of the scheduled clinic visits. (The exception is Germany, where telephone interviews occur, to discuss the record, as has been previously described.) A quiet space free from distractions should be provided along with ample space for displaying the food records and food visuals, or setting up the computer (if applicable).

Materials and Supplies

The following items are required for data collection:

- TEDDY Manual of Operations (MOO) (1 per interviewer)
- Food database user manual (if applicable)
- TEDDY 24-hour recall and 3-day food record forms
- The TEDDY Food Visuals Booklet:

- A Participant Copy of The Dietary Intervention Study in Children (DISC) Food Amounts Booklet (Metric version for European sites and English measurement version for the US sites)
- Selected images of food drawings and portion size photographs from *Matmallen*, a booklet of food shapes from *Livsmedels Verket* Publishers, which is used with dietary research in Sweden
- Country-specific pictures of infant formula packages, baby food packages, and packaging for dietary supplements. For US sites, it is recommended to utilize specific company websites for up to date product information.
- UK Food Atlas – this is only a suggested food visual, it is not a required food visual to be used at each site. It is the decision of each site as to whether they would like to use this in their clinic or not. However sites should use one larger food atlas such as the UK Food Atlas as a backup in situations when the TEDDY Food Visuals Booklet is insufficient.
- TEDDY Visual Aids-US Sites: Food pictures, Infant Formulas and Children Supplement documents (see Diet Committee's section of the TEDDY Members' website at www.teddy.epi.usf.edu)
- Supplemental Coding Aids (for US sites): NDS Substitutions, FIB Coding Help, which includes combination foods (see Diet Committee's section of the TEDDY Members' website)

The TEDDY Food Visuals Booklets are provided to each of the TEDDY participants (except for German participants because they weigh their food instead) so that each participant can have a copy with instructions for home use for the subsequent 3-day food records at 6, 9, 12 months and biannually thereafter.

Each site has access to electronic copies of the DISC Food Amounts Booklets, which are posted on the TEDDY Members' Website under the Diet Committee's section in the folder entitled "TEDDY Food Amounts Booklets and Matmallen Documents". There are two booklets – the first (Interviewer version) includes the serving sizes next to the pictures and copies of this should be used by each interviewer. The second (Participant version) is included in the TEDDY Food Visuals Booklet and does not include serving sizes next to pictures.

A second collection of documents are provided on the TEDDY Members' Website under the Diet Committee's section in the folder entitled "TEDDY Food Amounts Booklets and Matmallen Documents". The Matmallen documents are a translation of the drawings and photographs; each drawing and/or photograph is translated into grams for data entry into the specific database.

24-hour food recall and 3-day food records should not be collected without the Food Visuals Booklet present during the interview. If a TEDDY family discards or loses the TEDDY Food Visuals Booklet, a replacement should be mailed to the participant prior to collecting the 3-day food record.

Additional aids for food amount estimation include baby bottles (multiple sizes), baby bowls (multiple sizes) and baby food jars (multiple sizes) available for the primary caretaker to view to indicate amount given to the child. These are optional items and vary by country and clinic site.

12.6 General Guidelines for Working with TEDDY Participants

TEDDY families and children have made a commitment to participate in a long-term clinical study which involves a considerable amount of time and effort on their part. The diet study involves preparation of forms and accurate recordkeeping of food intake in a manner that takes time and energy and is not part of normal routine for most people. TEDDY staff must recognize the efforts put forth by the families and be prepared to answer questions about food in a timely and supportive manner. TEDDY clinic staff should strive to cultivate relationships with families that promote cooperation, compliance and continued enthusiasm for submitting TEDDY food records.

Motivation

Because the primary caretaker (e.g. mother, grandmother, father, etc) of the TEDDY child is the primary respondent for the TEDDY 24-hour dietary recall and the 3-day food records, it is important for the dietary interviewer to be able to motivate her/him to provide complete and accurate information. The dietary interviewer must always remain neutral and not let anything in words or manner express criticism, surprise, approval or disapproval related to the primary caretaker's responses during the dietary interview, especially when the caretaker reports consumption of "stigma" foods, such as high-fat, high-sugar items. Interviewers should be sensitive to the Primary Caretaker and adapt their style and approach to make her comfortable.

Every effort should be made to keep 24-hour dietary recall and food record collection as objective and non-judgmental as possible. The interviewer should avoid congratulating the primary caretaker for giving their child certain foods or reacting with dismay to reports of other foods. The interviewer can stress that he/she wants to know what the TEDDY child really ate and that honesty is appreciated. Dietary interviewers must maintain a demeanor of neutrality to all participants. The dietary interviewer should look for both verbal and non-verbal responses, be a good listener, and thank the participant for the information provided.

Privacy & Confidentiality

The dietary interviewer will gain trust by assuring the primary caretaker before each dietary interview (recall or food record collection) begins that everything the participant says is confidential and dietary intakes are not discussed with other participants. Any necessary discussion between site lead nutrition person and dietary interviewers about a specific 24-hour dietary recall or food record should be conducted in private, away from other participants or parents.

Interview tools and techniques

1. Using a script

A standard script is used to introduce the 24-hour dietary recall interview and start the recall process. The script provides continuity between interviews. TEDDY introduction scripts for in person recalls and food records are provided in the sections below.

2. Use of the TEDDY Food Visuals

Participants are allowed to freely select from items in the TEDDY Food Visuals Booklet and any food container display. Coaching in the use of this booklet will occur as needed during each interview to make sure that these tools are used appropriately. Participants should be allowed to select the most appropriate picture but interviewers may suggest additional options if the participant needs assistance or chooses an unreasonable option. Notes should be made to indicate how the amount was estimated.

3. Guidelines for probing

Probing is the technique used by the interviewer to stimulate discussion and obtain more information. Dietary interviewers probe when a participant's answer is not meaningful or is incomplete, i.e., when it does not adequately answer the question, or when the participants non-verbal language suggests doubt or misunderstanding.

Probing can be used to gather information about additional meals and snacks as well as additions to reported foods. The quality of the interview depends a great deal on the interviewer's ability to probe meaningfully and successfully. Probing techniques are covered extensively in the dietary interviewer training workshop and the training videos on the TEDDY website.

4. Unconsumed portions

The amount the child actually consumed is what should be recorded, not what he/she was served. Double check to ensure that the amount reported is what was consumed. Asking "*Was she able to finish that*?" or "*Did he eat all of it*?" helps to identify and eliminate the unconsumed portions. Additional prompts that could be used in this age group "*How much of the cereal ended up the floor, face, and high chair/table*?"

5. Unusual portions

If something sounds unusual, the dietary interviewer should question it and not accept the initial response. Redirecting questions and presenting appropriate alternatives from the food visuals permits the participant to restate her initial response and allows the interviewer to verify, confirm, or correct an unusual portion. Confirmation of any unusual intake or portions should be documented by stating which picture was used. Specific information about confirming portions and documenting unusual portions will be provided at the training workshops and at other training meetings.

Minimizing Response Burden for Participants

As a general rule, the dietary interviewer should accept the primary caretaker's level of detail or opinion about the foods and beverages eaten. When primary caretakers would not be expected to know the answers to prompts, especially regarding preparation methods or other details as part of a feeding, for example, at a birthday party or restaurant food, interviewers should record "unknown". Asking too many questions that cannot possibly be answered may lead the primary caretaker to respond inappropriately just to provide an answer to the question.

1. Unknown brand name products and fast food items

If the dietary interviewer is unable to locate a food item that is a national brand name product or a food from a national fast food restaurant chain, as much information as possible should

be recorded and forwarded to the lead nutrition person. A resolution will be provided by the site lead nutrition person. If the lead nutrition person is unable to obtain sufficient information about an unknown food, he/she sends an email to the nutritionist at the DCC to request further clarification and resolution, the DCC nutritionist provides the site with the resolution and the site updates the dietary data and submits the data to the DCC by following the instructions outlined in the Data Transfer section of this chapter.

2. Frequently consumed foods and beverages

Because infant formulas and baby foods are a common part of the infant diet, it is helpful for the dietary interviewer to visit the local supermarkets and become familiar with the many infant foods, dietary supplements and formulas available. During the interview, each dietary interviewer has photos of products and a listing of common national and local infant formulas and foods. These images and listings are posted on the TEDDY website for quick reference at the clinic.

3. Vitamins and/or minerals dietary supplements

Vitamin and/or mineral dietary supplements should be recorded. It is helpful for the dietary interviewer to visit the local pharmacies and websites that promote supplement sales to become familiar with the many infant dietary supplements available. During the interview, each dietary interviewer has photos of products and a listing of common national and local infant and child dietary supplements. These images and listings are posted on the TEDDY website for quick reference at the clinic.

4. Portion Sizes

Photographs of different portion sizes of cooked sliced meat can be used to assist participants in describing the portion consumed by the child. Food drawings can be utilized to represent cold cuts, sausage, meat loaf, or hamburger patties because the same volume for these items will have different weight.

It should be recorded if the meat portions include either bones or fat, and if the fat was eaten, consequently, the dietary interviewer should clarify with the TEDDY child's primary caretaker if the amount of food envisioned by looking at the picture of meat or fish includes bone or other refuse.

In many cases, infant cereal is measured in terms of tablespoons or perhaps bowls. The size of the bowl (which will likely be smaller than standard) should be recorded. When volume measurements are being used to describe non-liquid foods, the interviewer should describe an amount unit (e.g., deciliter, cup, teaspoon, tablespoon), and then the quantity and form in which the food was eaten (e.g., sliced, diced, solid). The form determines the amount that can be placed in a particular container and factors in the density of the food item. For most beverages, the interviewer should ask if the amount included ice, consequently the dietary interviewer should clarify if the level the primary caretaker points to includes ice.

Exception Procedures for German TEDDY Participants Living Outside of Munich

Research-trained personnel, mainly a nutritionist located at Munich will visit families for the 3-month TEDDY clinical visit at their home and will meet their paediatrician also. This is the only visit in Germany where the participating family meets the TEDDY nutritionist face-to-face. At that time, the nutritionist trains mothers (and/or other caretakers) in completing 3-day food records. The use of a scale is explained to the family. Families are advised that for

the 6-month and subsequent food records, they will send their food records to Munich by mail immediately after they are completed. From Munich the records are sent to Dortmund.

Procedures for Swedish TEDDY Participants

Study nurses see the TEDDY participants on all clinic visits. Study nurses give out and collect the 3-day dietary record and conduct the 24h- recall for participants. At the 3-month TEDDY visit, the nurses instruct participants on how to fill out 3-day diet records. The nurses also give families copies of the TEDDY food visuals to take home. When the family brings the 3-day food record to clinic, the nurse reviews the record with the family and provides the dietician with the printed record. A dietitian reviews the 3-day dietary record and obtains any supplementary information from the participant, either in-person during the visit, or via follow-up telephone call.

12.7 Instructions for Collecting the TEDDY 24-hour Dietary Recall

The 24-hour recall should be conducted after the interview at the 3 month clinic visit, with the exception of Germany, where the 24-hour recall is done at the participant's home.

Recording Meal Time

In general, the approach to collecting the 24-hour dietary recall is to find out when the child eats and what is actually eaten, versus asking what they ate for specific meals. Considering infants and toddlers eat multiple times throughout the day, dietary interviewers should strive to retrieve the time of every eating occasion because they are objective compared to the subjective definitions of meal names. When primary caretakers are not able to provide the time of meals and snacks, dietary interviewers may use the following probes to elicit times:

- *In general, how far apart are her meals?*
- *In relation to your own meals?*
- *When/if she woke at night– did you feed her?*
- *Did she have naps during the day?*
- *Did you feed her exclusively – did someone else give her a bottle, etc?*

Recording Meal Name/Location

Typical meals are -- Breakfast, Lunch, Dinner/Supper, Snack, and Other. For a 3 month old, the most likely "snack" or "other" may be used for in-between meal feedings.

Typical locations are -- Home, Day Care, Grandparents' Home, etc. For a 3 month old, it seems the most important options would be home, or daycare. Collecting information on the location of the meal will aid in the food description process. For the TEDDY study only, meal location is defined as the location of meal consumption.

The interviewer probes for missed meals, beverages and snacks and any other information that was inadvertently omitted. Edits are made as needed and notes are provided.

Portion Size Estimation

Obtaining portion sizes can be one of the most challenging aspects of obtaining the food intake record. Among breastfeeding mothers, it is even more challenging, since there is no

simple way to know how much milk the mom is producing and the child is drinking during each feeding.

The visual aids (discussed previously in this chapter) will be very important to use for both the 24-hour recall and the 3-day food records. The German TEDDY site will use the visual aids only for the 24h recall, the German families are asked to weigh the foods and record the weights of foods eaten.

Using Notes

Notes are used to clarify contradictory, questionable or unusual food items or amounts, or document cases where typical companion foods are not consumed. Notes serve as communication between the dietary interviewer, the site lead nutrition person and the nutritionist at the TEDDY Data Coordinating Center.

A meaningful note should be added to explain how the large amount was determined to be correct. For example, if the dietary interviewer enters 6 cups of ice cream, the note should describe how the girl determined that she ate 6 cups and the number 6 should be re-typed in the note field to ensure that a typographical error did not occur. Perhaps the girl reported two 3D bowls of ice cream for a total of 6 cups. Further probing might reveal that the ice cream was scooped into the bowl and consequently a deduction in the 6 cups to account for the air space between the scoops will needed to be factored in. Redirecting the participant to the food visuals for measuring cups might result in a more realistic amount.

Important information to include in notes includes TEDDY visual picture and size used to estimate unusually larger or small portions, missing condiments, and modifications of food such as removing the pears or cherries from a preparation of fruit compote. In the US, notes are also used to document standardized substitutions made for missing foods and conversions of portion size units.

Notes allow the site lead nutrition person to make appropriate changes to the recall to reflect what was actually eaten as well as confirming that the interviewer entered what the participant reported.

Using the TEDDY Food Visuals with Food Specific Units

Food specific units are most frequently used for packaged items such as one piece of hard candy or an ice cream bar. However, foods that may seem “standard” can come in several sizes (e.g., nugget, regular, extra large). In general, it is preferable to have the primary caretaker describe the portion consumed using the TEDDY Food Visuals Booklet. Because the use of visual aids often results in using dimensions and suggests entering the food using a shape, the dietary interviewer should look at the dimensions associated with the food specific units to get a sense of how realistic the dimensions reported might be.

It is important NOT to use the designations “small”, “medium”, and “large.” TEDDY is striving for consistency in reporting food data across four countries and many different cultural perceptions of size. Often times the consumer’s perception and country-specific food database definitions for the terms “small”, “medium”, and “large” vary widely, especially for round-shaped foods such as apples and cookies. Utilizing the TEDDY Visual Aids, therefore, is required to retrieve specific shapes and quantity from the interviewee which will help optimize data quality. The US sites have, in particular, standardized the measurements of Matmallen circle visual aids for NDS data entry.

MatMallen Circle Visual Aids US Standard Sizes (picture number, size in inches)

Round shaped bread cookies, and cakes	
A6	3.00
B6	2.25
C6	1.75
D6	1.13
E6	3.75
F6	4.25
J6	4.75
Fruits	
K8	4.10
F8	3.25
G8	2.38
H8	2.00
I8	1.63
Meats	
A1	3.00
B1	2.25
C1	1.75
D1	1.13
E1	3.75
F1	4.25
J1	4.75

Weight & Volume Measures

Weight measures should be used if the exact weight is available from a package label or if the Primary Caretaker reported an amount using one of the product images.

Volume measures are used to describe amounts for all liquid items, beverages, soups, and non-liquid foods served or quantified in bowls, cups or glasses. Examples in the TEDDY food visuals include the pictures of measuring cups and spoons, bowls and glasses. This will be a very common unit of measure for the TEDDY protocol because most of the food is given in bottles at the time of the 3 month visit. Primary Caretakers will be prompted to record the size of the bottle (in fluid oz or ml) and whether the child drank all or a portion of the bottle (and the size of that portion).

If the food amount is estimated without the use of the TEDDY Food Visuals Booklet, it is advised that volume measurements (cups, teaspoons, tablespoons) be used unless the parent is reading a food weight (ounces or grams) off a package or food label.

Estimation of breast-milk intake

If the child is breast-fed, the dietary interviewer should record each episode of breast-feeding. It is not necessary to record how long each episode of breast-feeding was. For

breastfeeding mothers, interviewers will not ask about the quantity of milk consumed at the breast. However, if the mother has pumped breast milk for later use and the infant drinks human milk from a bottle, then a specific portion size can be obtained. The interviewer should ask the mom to indicate the size of the bottle and amount the baby consumed.

Otherwise, the interviewer records an amount of breast milk that is: the US and Germany will enter 0.01 ml in their food databases and Finland and Sweden will indicate 0 ml (non-default value) in their food databases. This clearly inaccurate amount will be used as a "flag" by the DCC, and calculations of estimated breast milk volume intake will be made at the DCC. Calculations are based on algorithms developed by the Institute of Medicine (IOM) (*Dietary Reference Intakes for Energy, Carbohydrates, Fat, Protein, and Amino Acids - National Academies Press 2005*). These guidelines estimate caloric need based on energy requirements for weight and age, plus the estimated amount of incremental calories needed to support tissue accretion. The TEDDY child's weight is measured at the time of the clinic visit, and this weight is used in this calculation.

The IOM guidelines are based on analyses of pooled breast milk and metabolic studies which suggest that mean maternal milk production is 0.78 L/day from birth to month 6, and 0.6L/day from 7 to 12 months. Energy density of human milk is given an energy value ranging from 0.64 to 0.74 kcal/g, from studies using bomb calorimetry analysis. The IOM therefore adopted an average value of 0.67 kcal/g, and suggested that infants receiving human milk from months 4 to 6 would have an energy intake of 500 kcal/day based on average milk volume of 0.78 L/day, and average energy density of 650-670 kcal/L. The final algorithm adopted by the IOM is shown in the table below.

Where: EER = Estimated Energy Requirement
TEE =Total Energy Requirement (for tissue maintenance)
Energy Deposition = Additional kilocalories needed for tissue accretion

EER for Infants and Young Children

EER = TEE + Energy Deposition

0–3 months	**(89 × weight of infant [kg] – 100) + 175 (kcal for Energy Deposition)**
4–6 months	**(89 × weight of infant [kg] – 100) + 56 (kcal for Energy Deposition)**
7–12 months	**(89 × weight of infant [kg] – 100) + 22 (kcal for Energy Deposition)**
13–35 months	**(89 × weight of child [kg] – 100) + 20 (kcal for Energy Deposition)**

12.8 Interview Scripts for the 24-hour Food Recall

In the majority of cases, the 24-hour recall will be done as an in-person interview. The script for this interview is included below.

Introduction: The interviewer may or may not need to introduce self to the parent and thank the parent for participating in the TEDDY Study, depending on the context and sequence of the dietary interview with the rest of the TEDDY visit. The interviewer should be friendly and relaxed. The interviewer should always give neutral responses to whatever the participant says.

In introducing the 24-hour recall environment, the interviewer may use the following script as an example:

"In the past, many studies have tried to look at a baby's diet to learn more about how foods are associated with diabetes, including the development of diabetes and protection from diabetes. Many of these studies have looked at diet after diabetes has been diagnosed, which is more difficult to remember. TEDDY, however, will collect this information from you as we go along so the information reflects what [child] has actually eaten. To do this, I will collect the 24-hour dietary recall, where you tell me everything [child] had to eat and drink during the past 24 hours."

"Everything you tell me is confidential; there is not a wrong or right answer. TEDDY is only trying to develop a clear picture of [child's] diet. The recall will take about 30 minutes. OK?"

"Do you have any questions for me?"

The interviewer proceeds by asking the Primary Caretaker to make a list of all the foods and beverages the TEDDY child had yesterday, as follows:

"*We will first make a list of the foods and beverages [child] had from 12 a.m. yesterday until 12 midnight last night. This includes everything, including all milk, formula, other beverages, including tap water, as well as sampling of foods. I will also ask you about any vitamin, mineral or other supplements that [child] may have taken."*

"Do you have any questions? (Pause, wait for, and respond to questions.)

Before beginning the recall, the interviewer proceeds by reviewing questions 9-12, 14-15 on the 3-Month Interview:

"*Just thinking about yesterday":*

Questions #9-11:

"Was [child] exclusively breast fed, formula fed, or receiving formula and breast milk the whole day?"

If baby received formula:

"Did the baby have the same formula all day?"

Question #12:

"Did [child] receive any water?"

If baby is given water. Be sure to prompt for water when you conduct the recall.

Question #14:

"Did [child] receive any dietary supplements?"

If baby is given dietary supplements, be sure to prompt for the dietary supplements when you conduct the recall.

Question #15:

"Did [Child] have any other foods or drinks, including tiny tastes?"

If baby was given food, drinks, or tiny tastes, be sure to prompt for these when you conduct the recall.

"When we do the recall try to remember to include <list which things they said baby received above."

Keeping the answers to the above questions in mind, interview now proceeds:

"I will ask you questions to help you remember what [child] ate yesterday, so the information about [child]'s diet can be used for TEDDY."

"We realize [child's] diet is pretty simple right now, but we do want to get an idea about how often s/he feeds. I will ask you to tell me an approximate time [child] had each item. For example, "At 8 a.m., [child] had this, at 10 a.m. [child] had that." I will ask you where [child] ate this meal (home, daycare, restaurant). We will make a general list at first and then we will go back and fill it in with more detail. In the future, we will go through the list once more to make sure we have not missed anything, but [child's] diet is not as complicated as it will be later on so we'll skip this step today. We can use these (refer to amount estimation tools) to estimate the amount of what [child] ate yesterday."

"Were you the only person feeding your child yesterday?"

If participant answers yes, then say:

"Then all you have to remember is what you gave your child."

If participant answers no, then say:

"Then let us know which meals you provided and which meals the other person provided. We will ask you to remember as much as possible about what you fed your child as well as what the other person gave your child to eat. If you want to check your notes/records after the clinic visit, that would be fine – I'd be happy to give you a call later to clear up these meals. If you prefer to use email, we could correspond that way to clear up these items."

"Do you have any questions before we begin?"

If the response is no, reply "OK".

"Take a moment to think about yesterday, what you did, where you went and so forth. Thinking about the day can help you to remember what you and [child] did yesterday and when [child] ate."

"Now, let's begin."

"After midnight, when was the first time [child] had something to eat or drink?"

Record response then as needed say:

"What did she/he have at that time?"

The interviewer enters the information reported by the Primary Caretaker. Above all, the interviewer should let the Primary Caretaker think and say what ever comes to mind about

the previous day's intake, avoiding interruptions that may be distracting to the Primary Caretaker.

The interviewer verifies all of the foods recorded thus far and probes for missed items by reading the list back to the Primary Caretaker and asking:

> *"I am going to read back what you have told me. Let me know if you want to add or change anything. Can you think of anything else _____ ate or drank yesterday that we haven't put on the list? Do you remember if she/he woke up during the night and had anything to eat or drink? (if infant was under the care of others, you can add…) Also, did you include things that _____ ate when they were with their [father, babysitter, grandmother, etc]?"*

Meals that were given by someone other than by the Primary Caretaker should be flagged to see if the parent can accurately recall what the infant ate. If he/she cannot, then we offer that he/she can go home to check and we would give them a telephone call later to collect this information about these particular meals. Any errors should be corrected, and any additional foods the Primary Caretaker may report are added at this time.

Collecting Meal Information Detail: The interviewer uses this opportunity to ask questions about meal time, meal name and meal location if this information was not provided earlier. The interview should also prompt for things that seem to be missing (i.e. water, dietary supplements, food or drinks other than formula or breast milk, and tiny tastes that were listed in the 3-Month Interview questions).

The interviewer begins:

> *"Next we'll go over our list and I will ask you some questions about each meal your child had. You can use the TEDDY Food Visuals Booklet at any time to let me know much [child] ate/drank. You can also look at our display of commonly used jars and bowls to get an idea of how much [child] had."*

Exclusively Breast Feeding:

If baby is exclusively breastfeeding, ask the following for just one meal:

> "*Did [child] have all of his/her meals directly from your breast or from a bottle"*

If baby fed from bottle:

> "*Did you add anything to the breast milk?"*
>
> *"How much did [child] drink?"*
>
> *"Was s/he able to finish that?"*

Exclusively Formula:

If baby only received formula, continue with script below for one meal. Assume same preparation for all other meals.

> *"How was the formula mixed?"*
>
> *"Did you add anything to the formula besides water?"*

The interviewer asks the additional questions until a "no" response occurs. Then,

"How much did _____ eat (drink)?"

"Was _____ able to finish that?"

After collecting the details of formula preparation for one meal, ask only the following for the other meals:

"How much did _____ eat (drink)?"

"Was _____ able to finish that?"

Breast Milk/Formula & Other foods, drinks, vitamins

If the baby received other foods, drinks, tiny tastes, or vitamins, use the complete script for all meals:

"The first thing on your list is (the name of food)."

"Did you add anything to the (name of the food)?"

The interviewer asks the additional questions until a "no" response occurs. Then,

"What type of (insert name of food) was it? For formulas, baby foods and vitamins, you can look at our lists and pictures of the package labels to help you remember the exact food."

The interviewer continues to define the food, selecting food variables as required on each screen. Unknown should be entered if the primary caretaker cannot describe food in detail. Then,

"How much did _____ eat (drink)?"

"Was _____ able to finish that?"

Probe for things mentioned by participant at the beginning of the interview:

Earlier you mentioned that [child] received (water, dietary supplements, food, drink, and tiny tastes) yesterday. Do you remember, when s/he (drank water, took the supplement, and had the food, drink, tiny taste)?

Now the interviewer completes the trailer tab:

"Next (insert name of participant), in terms of the amount of food _____ ate, would you say this was close to the amount that he/she usually eats, a lot more than he/she usually eats, or a lot less than he/she usually eats?"

This question refers to the overall amount of food for the day, not the type of food. The dietary interviewer records the Primary Caretaker's response to the last question. In either case, the interviewer should ask and record why the intake was not usual. For example, the child was not feeling well and not eating much can result in eating a lot more or a lot less than usual. If needed, the interviewer can say:

"What makes you say it's (a lot more or a lot less than usual)?"

The dietary interviewer will determine the reliability of the data. If the dietary recall is unreliable because the Primary Caretaker was unable to recall one or more meals or for some other reason question the reliability, he/she will indicate this on the record. The interviewer does not ask the Primary Caretaker this question, nor share their opinion with them.

NOTE WELL:
The caretaker is asked to record the "first exposures" to key foods in a TEDDY questionnaire that the caretaker completes in advance of the 24-hour recall. In reviewing the 24-hour recall with the caretaker, the clinical staff should observe whether there are discrepancies between what the caretaker indicates on the questionnaire and what she or he reveals in the 24-hour recall.

Example 1: The TEDDY 3-month interview indicates the child has not yet been exposed to milk or dairy products, and the 24-hour recall indicates that the child had a taste of ice cream. In these instances, the clinical staff should resolve these differences and make adjustments in the questionnaire and/or 24-hour recall record accordingly. The clinical staff should keep in mind that the TEDDY study is interested in the smallest exposures; even a taste of a food should be recorded if it is the "first introduction" to the food of interest.

Example 2: The TEDDY 3-month interview indicates the child has not yet been exposed to milk or dairy products. During the 24-hour recall, it is reported that the child was given oatmeal porridge which contains oat and skim milk powder. In this instance, the clinical staff should resolve these differences and make corrections in the questionnaire and/or 24-hour recall record accordingly. The clinical staff should keep in mind that the TEDDY study is interested in the smallest exposures; even a taste of a food should be recorded if it is the "first introduction" to the food of interest.

The interviewer then thanks the Primary Caretaker and ends the recall by saying:

"Thanks so much for your help. Do you have any questions? (Pause, wait for and response to questions.) You did a great job and I really enjoyed talking with you."

At this point, the interviewer communicates to the participant about the upcoming 3 day food record for the 6-month TEDDY visit, with the following script:

"The diet information that we collected today will give us a good idea of what you child is eating right now. In order for us to measure your child's diet at other ages, we will be asking you to collect 3-day food records for the next TEDDY visit and for the upcoming visits after that. Instead of asking you to remember everything your child ate in the previous day, we want you write down everything your child ate and drank for three full days. It is like a diary. We want you to bring in this 3 day food record to your next clinic visit, and we will review the information with you just like we did today."

"Do you have any questions?"

"Your first 3 day food record should be done as close as possible to the baby's six-month birthday, and just prior to your child's next clinic visit. In order to get a good picture of what you child's diet is throughout the week, we would like you to include two weekdays and one weekend day in the food record. When you make your 6 month clinic appointment, we will give you the dates during which we would like you to do the 3 day food record."

"You have a copy of the TEDDY Book, right? Well, there s a pocket in the TEDDY Book for you to insert food package labels and boxes. When we complete the 6-month food record we will use the information from the packages and box labels to help make sure we are recording the right number of nutrients. If you give _____ any dietary supplements, we would like you to use the pocket in the TEDDY Book to collect those labels too. You don't have to use the pocket in the TEDDY Book. It may be easier for you just to bring in the bottles or packages, and this is fine too."

The interviewer then gives the primary caretaker a packet that contains the following materials:

- 3-day food record form and instructions
- The TEDDY Food Visuals Booklet
- if applicable, day care forms (which are site-specific) for the day care provider. Parents may request or sites may want to encourage parents to provide the day care provider with the TEDDY Food Visuals Booklet to use when completing the child's diet records.

In Germany the 3-day food record form is sent to the primary caretaker before the 6-months visit if the caretaker indicates the need.

Ending the 24-hour Diet Recall Interview

At the end of training, the interviewer says:

"Remember to keep the TEDDY Food Visuals Booklet and forms in a safe place because you will need to use them for the food record for the upcoming clinic visits. Feel free to call us if you have any questions when you are doing the food record."

Following up with Missing Food Recall Information

The caretaker is asked to follow up to obtain food information after the clinic visit if the infant was in day care (or in the care of someone other than the Primary Caretaker) in the previous 24 hours and the Primary Caretaker cannot recall with a reasonable amount of certainty what the child ate when he/she was not in their care.

The TEDDY clinic staff member who conducted the initial 24-hour recall interview is responsible for telephoning the caretaker later that day, or early the next day to obtain the missing food information. All meals that the child consumed not given by the Primary Caretaker are recorded and entered into the 24-hour recall record.

12.9 Instructions for Collecting the TEDDY 3-day Food Records

Primary Caretakers complete the 3-day food records at home and bring them to each of the TEDDY clinic visits from 6-months until 12 months and every six months thereafter until the end of the study.

NOTE: In August 2018, the collection protocol was changed so as to continue to collect 3 day diet records every 6 months from subjects who are single or multiple

persistent confirmed autoantibody positive (even if the subject reverts to autoantibody negativity) and to stop 3 day diet record collections on all other subjects after the 10 year visit. Should a subject be deemed single or multiple persistent confirmed autoantibody positive after the 10 year visit, the 3 day diet record collection will be restarted at the next visit. This will provide a complete dataset on all subjects up through 10 years of age and continued collection on persistent confirmed autoantibody positive subjects through the end of the study. Continued data collection on persistent confirmed autoantibody positive individuals will enable the TEDDY study to explore the role of diet, and dietary changes, through early adolescent years, on progression to T1D. It has been noted that the diet of individuals in this 10-15 year age interval is changed as compared to the diet at younger ages. These data will enable TEDDY to include these dietary patterns in assessments of T1D risk along with other exposures and changes occurring during the peri-pubertal period to include energy intake, energy expenditure, growth, hormonal changes and glucose demand. Epidemiological data points to increased T1D incidence during this period, TEDDY has also observed a declining rate of conversion from autoantibody negative to autoantibody positive (i.e., lower incidence of seroconversion during this age range). This reduces the statistical power to see an effect of dietary changes during the 10-15 year age range. Coupled with a lower compliance rate, as compared to families completing the 3 day diet record whose child is persistent confirmed autoantibody positive, it seems prudent to reduce the burden on families and clinic staff by discontinuing data collection after 10 years of age for families whose child is autoantibody negative. TEDDY will have a complete data set on this population through age 10 years so it will be able to address the contribution of diet in the cumulative incidence of islet cell autoimmunity up to this age.

NOTE: In 2020, it was decided that ALL 3 day diet record collections on ALL subjects would stop April 1, 2020.

The script for these 3-day food record interviews follows very closely to the script for the 24-hour food recall. The only difference is that there is a written record to help determine the prompts and questions about food intake. TEDDY staff members who collect 3-day food record information should be thoroughly familiar with the scripts and procedures described in the following sections of this chapter:

- Data Collection Procedures on page 11
- General Guidelines for Working with TEDDY Participants on page 14
- Instructions for Collecting the TEDDY 24-hour Dietary Recall beginning on page 17
- Interview Scripts for the 24-hour Food Recall beginning on page19.

The interview begins by thanking the family for their effort in the TEDDY diet study, explaining that the food information they provide will be of enormous help to the TEDDY research project. The Primary Caretaker and the diet interviewer should be in a private room together during all food record interviews. A sample script follows.

"We will use the food record that you brought in to make a list of the foods and beverages [child] had from 12 a.m. on [four days prior/beginning of diet

record] until 12 midnight [last night/end of diet record]. This includes all meals, snacks, beverages, including tap water, as well as tastes of foods. I will also ask you about any vitamin, mineral or other supplements that [child] may have taken during that time."

"As we go over your food record, I will ask you questions to help you recall information about what [child] ate, just to make sure we got everything."

"If you didn't write it down on the food record, I will ask you to tell me an approximate time [child] had each item. For example, "At 8 a.m., [child] had this, at 10 a.m. [child] had that." We will make a general list at first and then we will go back and fill it in with more detail. Finally, we will go through the list once more to make sure we have not missed anything. We can use the TEDDY Food Visuals Booklet to estimate the amount of what [child] ate on these days."

Abbreviated 3-day Food Records

As the interviewer reviews each page of the 3-day diet record with the Primary Caretaker, it may appear that foods look similar or repetitive. In this case, the interviewer may conduct the database entry part of the interview using the one day that is most inclusive of the foods consumed for all three days, then complete the remainder of database entry after the caretaker has departed. Continue as follows:

"We will use one day from the food record that you brought in to make a list on the computer of the foods and beverages [child] had from 12 a.m. on [four days prior/beginning of diet record] until 12 midnight [last night/end of diet record]. We will fill in any additional information we may need, including times, names, and locations of the meals. I will ask you for details about all meals, snacks, beverages, including tap water, as well as tastes of foods. I will also ask you about any vitamin, mineral or other supplements that [child] may have taken during that time."

"As we go over your food record, I will ask you questions to help you recall information about what [child] ate, just to make sure we got everything."

"Finally, we will go through the list once more to make sure we have not missed anything. We can use the TEDDY Food Amounts Booklet to estimate the amount of what [child] ate on these days."

After completing the database part of the interview, the interviewer should review the two remaining days with the Primary Caretaker to be sure that no foods, drinks, or meals were omitted, and that there is enough information to enter the records after the family has gone home.

Scan the record to pick out:

- time gaps
- foods that could be fortified, but are not listed as such
- quantities of food that are missing, very low or very high, or not descriptive enough
- meals where no beverages are listed

- incomplete preparation information or preparation not recorded in the day entered directly into the computer.

The interviewer should probe for confirmation or correction if any of the above items are noteworthy, recording comments on the paper record for later database entry. The following are examples of probes for the above situations. Use only as needed.

Time gap:

"You wrote that [child] had <list foods> at <time> and that the next time s/he had something to eat/drink was <time of next meal>. Can you remember if s/he had anything else to eat between <time> and <time of next meal>."

Fortified foods:

"You wrote that [child] drank orange juice. Do you remember whether it was any special kind – if any extra nutrients were listed on the label, like perhaps extra calcium? or "Do you recall if there was DHA added to the eggs that you purchased?"

Quantities of food:

Missing: *"Here you wrote that [child] had <food>, can you remember how much of that s/he was able to eat?"*

Very low or very low:
"Here you wrote that [child] had <low/high quantity> of <food/drink> (it may help to show them what the quantity looks like visually), *is that correct?" "Was s/he able to eat all of that?"*

Not descriptive:
Ex. "1 homemade cookie" Probe (using TEDDY Food Visuals Booklet):
"How big was the homemade cookie?"
Ex. "1/2 can of peaches" Probe: *"Were the peaches juice packed or syrup packed?" "Were those peaches drained?" & "What size was the can?*

No beverages:

"[Child] had <list foods in a meal> at <time>. Did s/he have any beverages with that meal?"

Incomplete preparation:

"How was the <food> prepared?"
"What type of oil did you use"
"Did you add anything to the <food/drink>?
EX: "Did you grill or fry the hamburger:

Once you have collected enough information, ask the reliability questions:

"Is this the usual amount that [child] eats or is this considerably more or less than usual?"

If more or less than usual"

"Why would you say it is more/less than usual?"

NOTE WELL:
The caretaker is asked to record the "first exposures" to key foods in a TEDDY Book section that the caretaker completes in advance of the clinic visit. In reviewing the 3-day food record with the caretaker, the clinical staff should observe whether there are discrepancies between what the caretaker indicates in the TEDDY Book and what she or he reveals in the 3-day food record.

Example: The TEDDY Book indicates the child has not yet been exposed to eggs or wheat, and the 3-day diet indicates that the child had a jar of Gerber Chicken Noodle Dinner. In these instances, the clinical staff would use the FIB Coding help document, which can be found under the Diet Committee's section of the TEDDY Members' Website to determine that the product contains chicken, peas, eggs, wheat and rice. The clinic staff should resolve these differences and make adjustments to the data extraction form and the 3-day diet record accordingly. The clinical staff should keep in mind that the TEDDY study is interested in the smallest exposures; even a taste of a food should be recorded if it is the "first introduction" to the targeted food.

After collecting enough information to enter the remaining days into the database **after** the participant leaves, thank the participant.

"Thanks so much for your help. Do you have any questions? (Pause, wait for and response to questions.) You did a great job and I really enjoyed talking with you."

Missing Information from Participants

In situations when the Primary Caretaker fails to bring in the food record, or brings in fewer than three days, the interviewer thanks the family for the amount of work they have already done. A sample script follows.

"This is a good start! Let's go over what you have already done. Once you have completed the rest of the days of the record, please mail it in, and we can go over it on the phone."

The interviewer then asks if the family had any specific questions or problems with completing the record. The interviewer asks the family to complete the remaining (or all) days of the 3-day food record, and provides a self-addressed, stamped envelope for mailing the records back to the clinic. The interviewer then informs the Primary Caretaker that the TEDDY clinic intends to follow up by phone to collect the missing days or other missing data. The interviewer then returns to the food record "as is", and reviews/records days that have been completed.

The TEDDY staff member who conducts the diet interview will make at least two telephone attempts to obtain the missing food record within the ten days that follow the clinic visit. If the missing information is not obtained after two of these telephone calls, the 3-day food record will be recorded "as is" with a notation in the data entry that there is missing information from the participant family or daycare provider.

Commented [A1]: I am not sure if this is standard. We have agreed in COL to call twice after the clinic visit is complete before considering it NOT DONE.

Specific Deficiencies in 3-Day Food Records

There are a number of circumstances where 3-day diet records may be deficient or incomplete. TEDDY has implemented a method for recording these deficiencies in the TEDDY Website tracking system (described later in this section of the MOO).

When speaking with families who submit deficient records, or missing information, the following procedures are suggested:

- **Record Not Done**: If the family does not return a 3-day food record at the clinic visit, request the record for the child's diet during *three days that occur within one week after the visit*. If is not possible to include a weekend day in this timeframe, the parent may complete the diet record and mail or fax the record to the clinic as soon as it is completed. The study nurse/dietary interviewer/nutritionist checks the record by phone as soon as it arrives at the clinic and resolves any questions in a follow up telephone call to the family. If clinical judgment indicates that the record is complete and reliable, the record should be entered into the database with a date of completion that corresponds to the date of clinic review. If clinical judgment determines that the parent is having trouble recalling the diet, therefore resulting in an incomplete or unreliable record, the diet record should not be entered into the database; and in this situation, the tracking system should be used to indicate that the a record was not received. The clinic reminds the caretaker of the time requirements and urges compliance for the next TEDDY visit. The center should retain the paper copy of the late diet record, placed in the subject's clinic file with a notation about the lateness and lack of data entry. The appropriate entry in the tracking system should then be made as described in the section below.
- **Record Not Complete**: If the family has completed the record only for 1 or 2 days, ask the caretaker to complete the missing day(s) within the same 7 to 10 day period and procedure specified above. The appropriate entry in the tracking system should also be made as described in the section below.
- **Diet Record Cannot Be Reviewed Within 7-10 Days:** If the family submits a diet record that cannot be reviewed and verified by clinic staff within 7-10 days, the TEDDY clinical staff must evaluate the record for completeness and reliability. If clinical judgment indicates that the record is complete and reliable, the record should be entered into the database with a date of completion that corresponds to the date of clinic review. If clinical judgment determines that the parent is having trouble recalling the diet, therefore resulting in an incomplete or unreliable record, the diet record should not be entered into the database; and in this situation, the tracking system should be used to indicate that the a record was not received.
- **Record Completed After TEDDY Visit Window Closes:** If the family completes a diet record with days that are after the TEDDY visit window closes, but within 7-10 days of the TEDDY visit, the record is acceptable and should be entered.
- **Record Completed 10 or More Days after TEDDY Visit:** If the diet record contains days that are more than 10 days after the TEDDY visit, thank the parent, and remind the family that diet records must be received in a timely fashion**.** If clinical judgment indicates that the record is complete and reliable, the record should be entered into the database with a date of completion that corresponds to the date of

clinic review. If the record is not complete and/or reliable, the late record will not be entered and the reason why it was not received should be indicated in the tracking database.

- **Weekend/Weekday Non-compliance:** If the family has completed the record without weekend days or with more than one weekend day, or with two weekend days and only one weekday, accept the diet record and enter data into the food database, but explain to the family that in the future, TEDDY needs food records covering 2 weekdays and 1 weekend day. The appropriate entry in the tracking system should also be made as described in the section below.
- **Part of Record Submitted Late**: If days 1 and 2 of the diet record have been received in a timely manner, but day 3 arrives later, outside the TEDDY visit window, thank the parent for their effort, and remind the parent that diet records must be received in a timely fashion. Do not include the late day or days in the food database file unless the clinical judgment indicates that the record is complete and reliable. The center should retain the paper record in the subject's clinic file with a notation about the lateness.
- **Record Complete but Not Submitted**: If a 3-day diet record is completed within the TEDDY visit window, but the caretaker forgets to bring it to clinic or otherwise does not submit it on time, thank the parent for the effort, and remind the parent that diet records must be received in a timely fashion. The nutritionist and interviewer at the clinical center should evaluate the record in the context of the child's age, reliability of the caretaker in past TEDDY visits, and prior diet record completeness. If clinical judgment suggests that the record should be accepted, then enter it into the food database with a notation about the time lag between the date the record was made and the date it was submitted to the TEDDY clinic. If the nutritionist is not confident that the record is reliable, do NOT include it in the food database. The center should retain the paper record in the subject's clinic file with a notation about the lateness and lack of data entry. The appropriate entry in the tracking system should also be made as described in the section below.
- **Missing Information**: A 3-day diet record could be submitted within the TEDDY visit window, but is missing foods or meals that the caretaker is not able to provide upon probing. In these cases, thank the caretaker, but only enter the fully completed days in the food database. If all three days have incomplete foods or meals, thank the caretaker but do not include any part of the record in the food database. The center should retain the paper record in the subject's local file with a notation about the incomplete information. The appropriate entry in the tracking system should be made as described in the section below.

Collecting Dietary Data at Day Care Facility

The interviewer should explain that the day care food record form is to be used if the child goes to day care or is in the care of someone other than the primary caretaker for more than four hours on any given day during the food recording period. The primary caretaker, in this case, will provide the day care staff or another care provider with the day care food record form (Appendix B), instruct the person(s) to record what the child eats and drinks while

under their care, and explain that they are welcome to contact the clinic if there are questions about how to fill out the form.

Parents may request or sites may want to encourage parents to supply the care provider with the TEDDY Food Visuals Booklet in order to assist in the recording of the amounts of food consumption. It is also recommended that the care provider use a known-size spoon to serve foods to TEDDY participants which potentially increases the accuracy of portion size estimation.

Because of privacy considerations (and HIPAA regulations in the USA), the parent may not want to inform the day care provider that the child is at higher than normal risk of type 1 diabetes and is participating in the TEDDY study. Accordingly, the day care form included in Appendix B contains no information that would reveal the reason why the caretaker wants to obtain the child's day care food record. If the parent expresses reservation about giving the form to the day care provider, ask the parent to telephone or visit with the day care provider to obtain the information. The caretaker can then complete the day care form himself/herself and bring it to the TEDDY visit.

Hand-written food records are strongly preferred in the TEDDY study even when the day care form is used. However, considering day care staff supervises multiple children at the same time and may not be able to monitor closely the intake of one particular child, the alternative method of documenting food consumption in such situation is the photographic food record.

Photographic food record requires the day care provider taking pictures of all foods and beverages served to a child before and after eating, as well as recording the time of consumption and the name for menu items. Due to the inaccuracy in recognizing foods and estimating portion size photographically, this approach is only suggested when the day care staff foresees the impossibility of describing food consumption adequately on the day care food record. Given the agreement from day care staff to complete photographic food record, it is the parents' responsibility to ensure the day care staff has access to functional devices that are needed to take and transfer pictures. The TEDDY clinics will not provide devices.

The following items are needed to complete photographic food record:

1. A functional digital camera with flash light. The camera should be of at least 3 megapixel resolution. Digital cameras on cell phones are not recommended due to less desirable quality of the pictures.
2. A wooden or plastic clearly-marked ruler with a minimum length of 10 inches (25.4 cm). Metallic rulers are not recommended due to possible change in length under varying ambient temperatures. Silverwares are not recommended as portion size references because of inconsistent sizes. Soft measuring tapes are invalid to use.
3. A flash drive or a blank compact disc (CD) to store and transfer pictures.
4. A tripod may be needed to avoid blurry pictures.

Steps to complete photographic food record:

1. Make sure all devices function well.

2. The day care staff needs to attach a copy of the menu to the Day Care Food Record Form and mark the date and time of every eating occasion while the TEDDY child is under their supervision.
3. Food pictures need to be taken in well lit conditions for portions size estimation. Use additional lights if needed.
4. Take pre-eating pictures right after the food is portioned onto the serving plate or bowl. If the meal is served in the family style, take pictures before the child starts eating.
5. Place the ruler next to a plate with the marks facing up. If the dinnerware is oval- or rectangle-shaped, parallel the ruler lengthwise. Make sure the length and width of uneaten food is clearly indicated by the ruler. Place the ruler vertically to show the thickness of the foods, the depth of the bowl, and/or the height of a bottle / cup. Pictures need to show clearly the three (3) dimensions of solid foods and the volume of liquids.
6. Take pictures of all leftovers after the child stops eating, including untouched foods.
7. When photographing foods with multi-layers such as hamburgers or sandwiches, take one picture with the sandwich open (without the top slice of bread) and another picture of the closed sandwich to optimize portion estimation. This is required both before- and after-eating.
8. If more than one plates and/or bowls are used, take separate pictures of every single plate and/or bowl.
9. Save food label(s) if individually packed food is served. Such foods include sliced or string cheese, single-serving peanut butter crackers, and yogurt cup.

Transferring photographic food record:

The parents are in charge of collecting pictures and other intake-related information from the day care staff and transferring them to the TEDDY sites as soon as possible. Digital pictures are required and they need to be submitted prior to the scheduled visit so that the TEDDY staff can review in advance. No picture printouts will be accepted. The TEDDY staff at every site will reach an agreement with the parents regarding the method and timing of transferring pictures.

Management of photographic food record

The approaches of f submitting photographic food records to the DCC and record analysis are currently under discussion. This section is to be completed later.

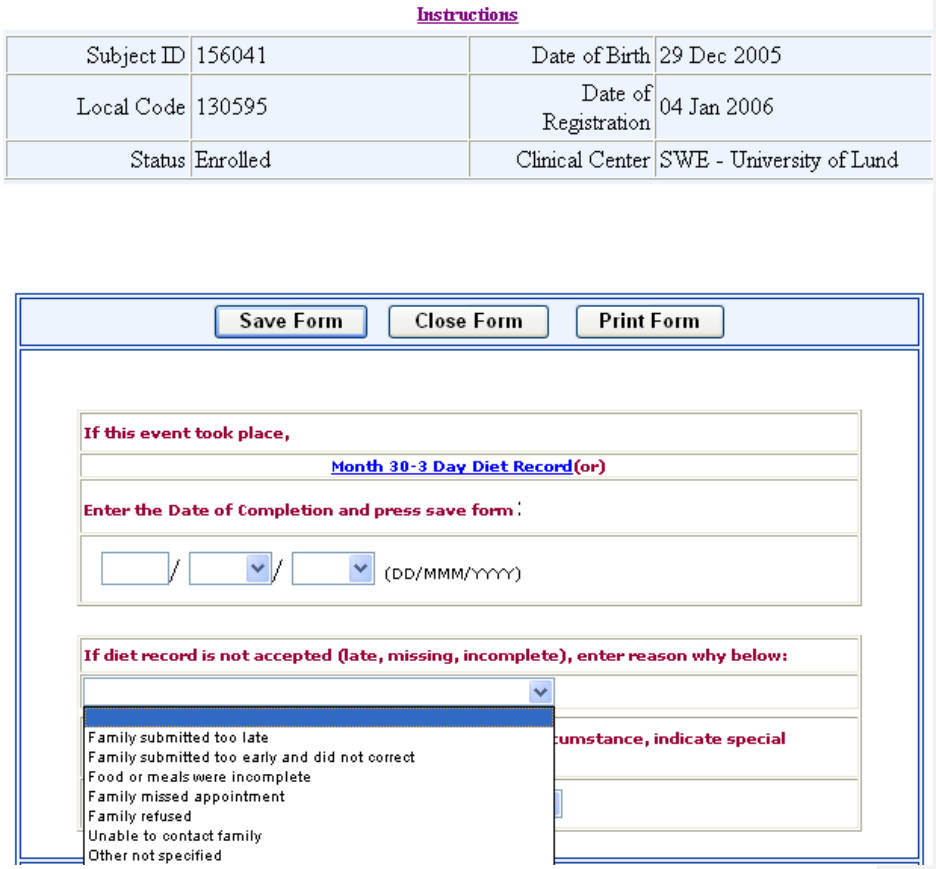
Tracking System for Exceptional Diet Records

The TEDDY study is capturing attributes related to diet records that are late/missing or otherwise deficient in order to help with analysis of data. The reasons why families submit these exceptional diet records are organized in drop-down boxes in each subject's record screen in the tracking system.

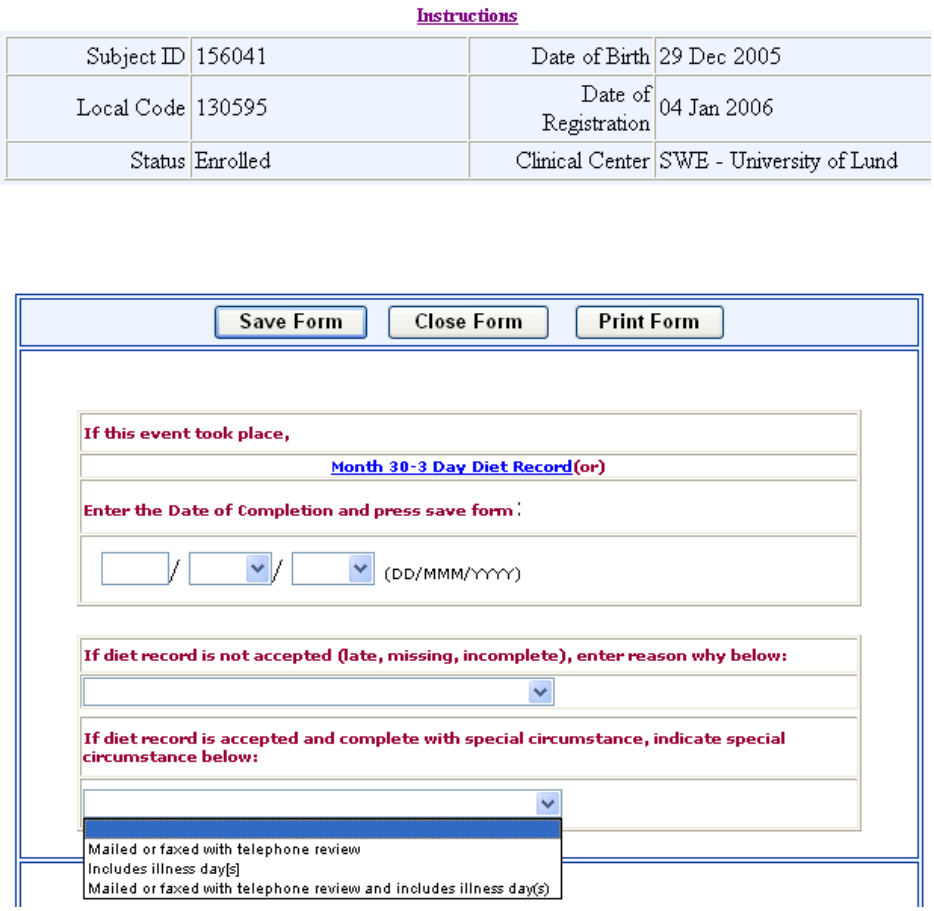
The instructions for using each screen for the tracking system are available online. This description here covers only those exceptional diet records as discussed above.

There are two drop-down boxes in the tracking system to record the reasons for deficiencies in diet records. Refer to the screens on the next page, as follows:

- **Box #1: Records that are late or missing and INCOMPLETE, NOT ACCEPTED**
  - Family submitted too late
  - Family submitted too early and did not correct
  - Food or meals were incomplete
  - Family missed appointment
  - Parent refused
  - Child refused
  - Unable to contact family
  - Other not specified



- **Box #2: Records that are ACCEPTED, COMPLETE with special circumstances**
  - Mailed or faxed late with telephone review
  - Includes illness day(s)
  - Mailed or faxed with telephone review and includes illness day(s)



Tracking System – Entry of Date of Completion

In the Tracking System there is a field to enter the "Date of Completion" of the 24 hour recall or the 3 day diet record. For the European sites "Date of Completion" means the date on which the 24 hour recall is completed with the parent or the day that the 3 day diet record is reviewed with the parent. For the US sites "Date of Completion" means the date on which

the 24 hour recall is completed with the parent and entered into NDS or the day the 3 day diet record is reviewed with the parent and entered into NDS.

> **NOTE WELL:** US sites only need to enter the "Date of Completion" for 3 day diet records that are accepted with special circumstances; US sites do not need to enter the date of completion for 24 hour recalls or 3 day diet records accepted without a special circumstance because the DCC can retrieve this date from NDS. European sites should enter the date of completion for all accepted 24 hour recalls and 3 day diet records (for 3 day diet records accepted with or without special circumstances).

Day Care Forms

The caretaker is asked whether the child attended daycare for more than four hours during the three-day period covered in the food record. If the answer is yes, then the interviewer asks the caretaker to provide a day care diet form. (Appendix B). The interviewer puts the form aside and then tells the caretaker that the day care form will be reviewed during the review of the other parts of the food record. If something on the day care record is unclear, either the day care provider will be called directly by TEDDY staff to obtain additional information, or the primary caretaker (mother) will be asked to obtain a clarification from the day care providers. This may depend on the privacy (HIPAA) considerations of each site. The parents are encouraged to leave a note on the record if the daycare / catering company can be contacted or if a phone call would be worthless. If the amount of consumption can not be reliably quantified, the food record from the same day is classified as incomplete and will not be entered.

Refer to instructions " Collecting Dietary Data at Day Care Facility" on page 31.

Editing the Recalls and Food Records

The dietary interviewer should review and edit the 3-day food record as soon as possible after its administration. Complete detail about the missing foods (or unknown foods) should be reviewed and edited to ensure that adequate information has been provided for the site lead nutrition person to make a resolution. Remember another person should be able to picture the reported food so information about the color, size, shape, ingredients, and preparations should be included in the note. Additional instructions that are specific to the nutrient databases are located in the appendices.

In Germany, the 3-day food record will either be mailed to the TEDDY clinic in Munich or the family will bring it in to the TEDDY clinic. The records will be quickly reviewed for completeness of days and for consistency with the "First Introductions" list . If additional days of food records are needed, the mothers will be called and asked to send more. Then, on a weekly basis, the completed records will be sent to the lead nutrition person in Dortmund. The lead nutrition person will check the record for content and will call the mother to go over the record over the phone. The record will be reviewed with the mother meal by meal.

12.10 Quality Assurance Overview

Study-wide quality assurance procedures, and procedures to remedy deficiencies in quality measures, are discussed below.

12.10.1. Onsite Quality Assurance

Dietary data collection, checking, coding and entering processes are standardized in each TEDDY country in a way that they promote producing information that is comparable across the countries. Onsite quality assurance is coordinated by lead nutrition persons who review the overall quality of the dietary data collected in the field. On-site quality control procedures will include these steps:

- There is a review (and corrections as necessary) of each dietary recall and food record, and mother's food frequency question (FFQ) by interviewer.
- There is a review of each dietary recall and food record form by the site lead nutrition person with feedback provided to the respective dietary interviewer.
- Each European site reviews 5%-10% of entered food record data (for each age group) for consistency prior to food and nutrient analysis.
- The US TEDDY sites review 10% of entered food records on a monthly basis. If diet records are processed by a new diet interviewer, all data need to be checked for approximately 6-8 weeks after training.
- There are periodical quality control observations of each dietary interviewer while they are interviewing a primary caretaker. Every site lead nutrition person will decide the frequency of such observations.

12.10.1.1. 24-hr recall or 3-day food record

12.10.1.1.1. Quality Control Observations

The 24-hour Dietary Recall and Interviewer Observation Forms (Appendix 12 E) are used to document activities related to the observation of the 24-hour dietary recall and collection of the food record. This form is completed by the country lead nutritionist directly following observation of a dietary recall. The 24-hour Dietary Recall and Interviewer Observation Forms are designed to document information on the quality of the interviewing style and to offer suggestions for improvement. Upon completion of the dietary recall observation, information is shared with the dietary interviewer.

At this time there is no research to indicate whether dietary interviews performed by nutritionists and those performed by nurses and other non-nutrition personnel will yield like results. This question among others will be addressed for quality assurance purposes.

12.10.1.1.2. Records Review

The dates when the food should be recorded are given in advance by study personnel, not left per choice of the primary caretaker. It is checked that the records are kept on the dates given. At the end of each collection, the dietary interviewer proceeds to review each 24-hour dietary recall and food record collected. Obvious errors may be corrected on the spot (e.g., entry of 10 peaches consumed when the dietary interviewer knows that it was only one.) Should the dietary interviewers have questions, they should discuss these with the site lead nutrition person to reach a consensus. Site lead nutrition persons may consult with the TEDDY DCC nutritionist for more information if needed.

At least once per week, the lead nutritionist reviews all 24-hour dietary recalls and food records collected for the site. The site lead nutrition person may make or recommend changes in the 24-hour dietary recalls and food records only after discussing the proposed change(s) with the dietary interviewer. It is the responsibility of the site lead nutrition person to document and communicate site-specific consensus decisions to the lead nutrition people within the specific country, to the DCC and to the dietary interviewers within his/her site.

Checking of the 24-hr recalls and 3-day records:

The interviewers and the research personnel in each country monitor the 24-hr recall and 3-day record data using similar principles. The following items should be checked for each form received:

- Does the food record contain 3 consecutive days (2 weekdays and 1 weekend day)? Are the dates of the food records indicated?
- Who of the study personnel received the record and checked it (ID recorded)?
- Is the 24-h recall or food record complete?
- When and where are the meals eaten?
- Type of the day (e.g. a sick day, day away from home)?
- Any unusual time caps between the meals?
- Are the foods eaten outside home (day care, school, during visits outside home) included?
- Number of foods/drinks on the record line? Only one item per line allowed.
- Is the origin of the food/drink obvious (e.g. homemade, commercial product)?
- Is the food/drink described explicitly so that the person entering the foods/drinks into the database is able to identify them correctly? Food/drink labels should be attached if necessary.
- Is the brand name and type of food/drink indicated (e.g. artificially sweetened vs. sugar-containing product). If a formula that has been prepared from powder or diluted from a concentrate the proportion of powder/concentrate and water should be given.
- Does every eaten food item have a portion size?
- Has the portion size estimated using the TEDDY portion size booklet or measured?
- Is the portion size unambiguous?
- Correct conversions from volumes to weights?
- Have all snacks been reported?
- Has the food preparation method of a meal been described (e.g. fried, baked, boiled etc.)?
- Is there enough information on the food items used
    - fat content (e.g. fat free milk vs. milk with a fat content of 2 % or more, whole milk yogurt 4%)
    - origin / source of the food (e.g. infant formula on cow's milk vs. infant formula on soy; cow milk vs. rice milk)
    - milk in food preparation vs. drunk milk
    - fat in food preparation vs. fat on bread
    - specificity of every food item used in food preparation (e.g. cereals, milk)
    - fortification of food items (e.g. milk with or without vitamin D)
- Is there enough information on recipes?
- Has salt been used or not in food preparation?

- Water drunk? Other drinks missed at a meal?
- Are some easily forgotten food items listed in the 24-hr recall or food record if they have been used (e.g. vitamin and mineral supplements, companion foods like butter or margarine on a slice of bread, milk with porridge, jelly/jam/syrup with pancakes, ketchup with French fries, buns with hamburgers etc.)?
- Has the child eaten/drank any foods/drinks/snacks on his/her own? Are they recorded?
- Is there enough information on the convenience foods used?
    - brand name
    - producer
    - ingredients
    - fortification
- Is there enough information on the vitamin and mineral supplements?
    - tablet, capsule, drop?
    - brand name
    - producer
    - ingredients
- Are the amounts of foods/drinks feasible and are only the amounts that the child actually ate included (leftover subtracted from the total amount)?
    - Common mistakes include such as typographical errors, such as 10 servings entered instead of 1 serving
    - Selection of inappropriate/incorrect forms of food, such as 200 ml powdered infant formula instead of 200 ml of diluted infant formula mixed with water

NDS specific notes (US sites):

- Portion size should be reasonable based on common serving size at the location of data collection. The preparation should be reasonable based on location (e.g., they should enter unknown for type of fat used to fry foods if purchased in a restaurant). Check for a reasonable size based on the reported location (e.g., school milk comes in ½ pt cartons in the USA)
- Incorrect conversion of fractions to decimals
- Correct documentation of conversion of user recipe foods that require serving sizes. For example, common serving size for infant formula is 5 fl. oz, if 4 fl. oz. was consumed, the data entry person may type in 0.8 serving with a comment specifying “4 fl. oz. drank”.
- Enter liquids as FO (fluid ounces) or ml (milliliters) instead of OZ (ounces) or grams
- Check the form of food (e.g., applesauce is 100 grams, ½ cup of turkey should be entered as cut pieces)
- Chicken is entered as food specific unit instead of dimensions
- Fruits and baked goods are entered in DIMENSION, not as small, medium or large

- Modifications of fast foods or mixed dishes (e.g., subtract off the pickle on a McDonalds cheeseburger if the note indicated the participant did not eat it).
- Correct documentation of NDS sub see document
- Correct documentation of food visual used for serving size

Helpful tips include shortcut to finding common foods in the database, probing strategies that have worked for others, additional questions that may help to gather information (e.g., to get information about food preparation ask if a food was cooked on top of the stove, in the oven or in a microwave to determine if it was baked, boiled or fried.)

German Quality Assurance Procedures

Many TEDDY participants in Germany do not receive regular face-to-face contact in clinic visits and they submit their diet records by mail to Munich. From Munich records are sent to Dortmund, to the nutritionist located at the FKE. The nutritionist checks the diet records and phones the families to ask for missing information Promptly after receiving the data. The nutritionist later codes the food records and enters 100% of the records into the database. The food records have been manually transcribed into a table prior to data entry. This step will be cancelled in the near future after an electronic ORACLE data entry system is activated. The lead nutrition person will search for abnormal energy intake values before transferring the SAS data files to the DCC.

As part of the non-diet portion of the TEDDY visit/call, information recorded in the TEDDY book is transferred to the TEDDY book extraction form by the study nurse/dietary interviewer/nutritionist. The study nurse/dietary interviewer/nutritionist then checks the 3-day food record form, as well as the putative corresponding form by the day-care provider as needed.

The interviewer reviews the form, using the TEDDY Food Visuals Booklet described on page 10 of this chapter to help identify portion sizes. The interviewer also reviews the labels and packages for infant formula, baby foods and/or dietary supplements that the caretaker has brought to the clinic. At the German site, primary caretakers will be asked to provide food weights to supplement their food portion estimates. When there is any uncertainty about the foods or drinks consumed at day care, the day-care provider will be telephoned by the primary caretaker or the primary caretaker (e.g. mother) will be asked to clarify.

Finnish Quality Assurance Procedures

When a new study nurse begins their work in any TEDDY clinic, a nutritionist educates her/him to the nutrition methods (24-hour recall and food diary) in TEDDY Study. The method and its main questions, including theoretical background of the study, advantages and disadvantages of the methods in use and the details how to do a 24-hour recall and to check food records, are taught. In addition, every study nurse practices with a nutritionist how to do 24-hour recalls and to check food records. The 24-hour recalls and food records done/checked by a new study nurse are double-checked by a nutritionist even more carefully after the forms are returned from the clinic. In any case, nutritionists double-check all the 24-hour recalls and food records before entering them into the food diary database and if necessary call the families for additional information. All new nutritionists do theoretical

and practical exams to reach similar level of precision in entering food records in the TEDDY Study in Finland.

All of the Finnish TEDDY participants meet the study nurses during the visits at the clinics. The nurses do the 24-h recalls and check the food records. The study nurses are trained by a nutritionist responsible for the quality of food records in Finland.

The 24-h recalls and food records are sent by post to Helsinki where the nutritionists check them and contact the family by phone if some important details are missing. Later the nutritionists enter the 24-h recalls and the food records into the database.

Swedish Quality Assurance Procedures

All of the Swedish TEDDY participants meet the study nurses during the visits at the clinics. The nurses do the 24-h recalls and check the food records. The study nurses are trained by a nutritionist responsible for the quality of food records in Sweden.

The 24-h recalls and food records are sent by post to Malmö where the dietitians check them and contact the family by phone if some important details are missing. Later the dietitians enter the 24-h recalls and the food records into the database.:

US Quality Assurance Procedures

TEDDY participants meet with the clinic staff during the visits at the clinics. The clinic staff members do the 24-h recalls and check the food records. The clinic staff have all completed NDS training are each responsible for the quality of food records in the US

Through out the month, the clinic staff performs random quality control checks of diet records. At least 10% of all diet records for the month are double checked before the project is transferred to the DCC.

12.10.1.1.3. Validity between the questionnaires: food recall/record vs. first introduction of foods

It is important to cross check frequently that the foods appearing in the diet records or in the 24-hr recall are also included into “the first-introduced foods” identified in the 3-Month Primary Caretaker Interview or in Teddy-book.

12.10.1.1.4. Mother’s Food Frequency question

Interviewers should check the food frequency information when receiving the mother’s questionnaire. Does the FFQ question have:

- frequencies that are blank

- lines with several inconsistent frequencies (e.g. once a day and twice a week given)

- frequencies that are not feasible (e.g. fish soup 10 times a day regularly)?

If yes, they should be corrected.

12.10.1.1.5. On-site checking of the processed TEDDY food record data

The Clinical Centers transfer dietary data to the DCC on a monthly basis after onsite quality assurance activities have been completed. On a monthly basis, the site lead nutrition person combines the food diaries and recalls into a computer file which is database-specific, and

submits the data to the DCC via e-mail. Upon receipt, the DCC confirms the successful transmission of the electronic file, and via e-mail notifies the person sending the data from each site accordingly.

The checking process of the food record outcome data on each site includes usually three stages. An example from Finland (outcome data varies slightly from country to country):

a. Composite dishes (food use class); checking of amounts of the dishes for validity and feasibility, e.g. if a 9 month old child has eaten 800 g of porridge for breakfast the weight of the dish is probably too large
b. Foods, food groups (ingredient class); in this stage the mistakes in recipes will be usually caught, e.g. if the child has eaten 100 g of meat-vegetable stew in a day and no other meat dishes during the same day and the food items listed include 2000g of ground beef, something must be wrong with one of the recipes or there is an error (e.g. typo) at data entry
c. Energy and nutrients; at this stage both the typing errors and the error in the food composition database will be checked in case of outlying values for a nutrient

The quality control will be carried out by age and gender, and by including outcome data from each of the three days food record separately into the data that is checked. Frequent monitoring of the data by interviewer should also be carried out on site.

Food level monitoring includes the checking of the highest values (highest 5%) and in the case of nutrients also the smallest values (lowest 5%). The goal is to detect the values that are clearly different from the others. SAS procedures (e.g. PROC UNIVARIATE: Stem Leaf, Box plot, Normal Probability Plot) are used in the detection of deviate values.

All the values that need checking or correction are listed and using the ID and the date of the food record the entered data of the child is re-visited and the explanation for the detected abnormal value is documented. The errors are corrected to the food record entry data and the analyses are re-run. The checking process is repeated regarding the values that were found incorrect in the previous run.

The Finnish, German, and Swedish data processed by the local food and nutrient calculation program are checked on site before sending to it the DCC while the checking of the US data is entirely done in the DCC (food and nutrient calculation done at the DCC). Only Finland submits a monthly file where the mean energy and nutrient intake is calculated per food record. Germany and Sweden submit files where each record entry (food/drink) is analyzed and the nutrient intake calculated by the entry level only. The DCC will calculate the sum of the energy and nutrients by day. The checking of the daily energy and nutrient intake in Germany, Sweden and the US is done at the DCC although it would be more desirable to have the checking done at the site for quicker feedback.

The lead nutritionist(s) at the DCC is responsible for monthly 'on-site' data checking of the US dietary data. Dietary intake data is calculated at four different levels by the NDS at the DCC, which results in four output files for the food record from any given day:

a. Component/ingredient level – energy and nutrient content of every recorded food broken down into core components and ingredients. For example, pasta sauce is broken down into ground beef, tomato puree, onions etc.
b. Whole food level - energy and nutrient content of the entire recorded food. The pasta sauce, at this level, is analyzed as one single food.

c. Meal level – energy and nutrient intake from every eating occasion (i.e., meals and snacks)
d. Food record level – total energy and nutrient intakes per every 24 hours.

Step 1: The DCC nutritionist(s) examines the "food record level" data file and looks for outlier values within gender and age groups.

Step 2: For abnormal energy and nutrient intake values detected in Step 1, the corresponding Subject ID(s) and date(s) of intake will be used to examine both the "meal level" and "whole food level" data files. The DCC nutritionist(s) will notify the clinical site(s) of questionable meals and/or foods, and the site(s) is charge of fixing the data based on original food records and re-uploading the NDS backup files to the DCC with "rev" noted at the end of the filename. Every site is given 30 days from the date of notice to complete data correction. The DCC will re-calculate energy and nutrient intakes upon receiving the revised NDS files.

Food record data files / nutrient data files:

It has been defined on pages 43-45 which variables should be included when sending data sets to DCC. Each site should check the dietary data before sending it to the DCC:

Special attention should be paid to following points:

1. Project and person IDs given.
2. Total number of the records?
3. Total number of children in the data set?
4. Total number of days in the dataset?
5. Less than 2 records per child?
6. More than 3 records per child?
7. The age-specific round of the record, is it correct?

12.10.1.1.6. Comparison of variation between interviewers

Each site will monitor the variation between interviewers by comparing the following food record means per day and per age group based on data collection/interviews from each interviewer: number of food record rows (food entries), intake of energy, protein, fat, saturated fatty acid, monounsaturated fatty acid, polyunsaturated fatty acid, carbohydrate, and sugar. If any significant differences between the interviewers will be detected the food records of the interviewers with distinct values should be checked and the results should be discussed with the interviewer. The results should also be reported to the DCC. Frequency of this monitoring scheme will be determined by each site

12.10.2. DCC Quality Assurance of the dietary data sent from four TEDDY countries

On a monthly basis, the site lead nutrition person combines the food records and recalls into a computer file which is database-specific, and submits the data to DCC via e-mail no later than the 25th of each month. Upon receipt, the DCC confirms the successful transmission of the electronic file, and via e-mail notifies the person sending the data from each site accordingly.

The initial onsite quality assurance activities should be completed by the dietary interviewers and data entry persons prior to data transfer. Detailed procedures are outlined from Page 48 of the MOO.

12.10.2.1. 24-hr recall and 3-day food record

Every three months the nutritionists in the DCC will spot check the energy and macronutrients (protein, fat, saturated fatty acid, monounsaturated fatty acid, polyunsaturated fatty acid, carbohydrate, and sugar) and intake levels of selected nutrients intake among the TEDDY countries by testing the means of these variables between study sites categorized by age and gender. Possible outliers will also be paid attention to.

Any clearly distinct or questionable values will be documented and the feedback given to the respective center.

The lead nutritionist(s) at the DCC is responsible for monthly external quality assurance after dietary data has been restored into the NDS and output to the SAS data files. Dietary intake data is calculated at four different levels by the NDS, which results in four output files for the food record from any given day:

a. Component/ingredient level – energy and nutrient content of every recorded food broken down into core components and ingredients. For example, a piece of chicken nugget is broken down into chicken meat and breading.
b. Whole food level - energy and nutrient content of the entire recorded food. The chicken nugget, at this level, is analyzed as one single food.
c. Meal level – energy and nutrient intake from every eating occasion (i.e., meals and snacks)
d. Food record level – total energy and nutrient intakes per every 24 hours.

12.10.2.2. Validation of the food records using Estimated Energy Requirements based on Weight and Physical Activity (not part of the frequent monitoring)

Step 1: The DCC will review data from each site, with particular attention to those records which reflect dietary intake that is in the top 5% and bottom 5% of estimated energy requirements as projected by the Institute of Medicine (IOM). (*Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes: Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids, National Academy Press, Washington, DC 2002*)

The rationale for this analysis is that reported energy intake (EI) may be expressed as a ratio of estimated energy requirements (EER). Values of EI: EER falling below the 95% confidence limit of agreement in these two measures signify the presence of underreporting, and those falling above the 95% confidence limit signify over-reporting. A formula for calculating the lower 95% confidence limit to assess external validation was proposed by Goldberg (the Goldberg cutoff) and it has been used by numerous authors to analyze dietary data (*Goldberg GR et al., Critical evaluation of energy intake data using fundamental principles of energy physiology. Eur J Clin Nutr 1991:45:569-581*). Detection of inaccurate energy intakes in TEDDY may be challenging, especially among older children, because the physical activity level is not determined in this study. However, the Goldberg cutoff can be used as guiding reference for quality control of the dietary data received at the DCC.*(Black AE. The sensitivity and specificity of the Goldberg cut-off for EI:BMR for identifying diet reports of poor validity. Eur J Clin Nutr. 2000;54:395-404.)*

Questionable foods, unreasonable amounts, or questionable total energy intakes are called to the attention of the site lead nutritionists, with a DCC recommendation regarding editing

when it is thought that the dietary interviewer made an inappropriate choice during data entry. Sites are contacted on a regular basis regarding any questionable items noted during the DCC quality control review. The queries serve to resolve the immediate questions and to alert the interviewers to the types of issues that are questioned and require confirmation.

In addition, the DCC will evaluate internal consistency by reviewing questions that should yield the same answer, such as participants' responses to questions about vitamin/mineral supplements, which is reported at two times during each TEDDY clinic visit -- in the TEDDY book and in the 3-day food recall.

Age- and gender- specific EER estimations are summarized below:

Age	Male	Female
0-3 months	(89 × weight [kg] − 100) + 175 kcal	(89 × weight [kg] − 100) + 175 kcal
4-6 months	(89 × weight [kg] − 100) + 56 kcal	(89 × weight [kg] − 100) + 56 kcal
7-12 months	(89 × weight [kg] − 100) + 22 kcal	(89 × weight [kg] − 100) + 22 kcal
13-36 months	(89 × weight [kg] − 100) + 20 kcal	(89 × weight [kg] − 100) + 20 kcal
3-8 years	88.5 − (61.9 × age [y]) + PA × (26.7 × weight [kg] + 903 × height [m]) + 20 kcal Where PA is the physical activity coefficient: PA = 1.00 if PAL is estimated to be ≥ 1.0 < 1.4 (sedentary) PA = 1.13 if PAL is estimated to be ≥ 1.4 < 1.6 (low active) PA = 1.26 if PAL is estimated to be ≥ 1.6 < 1.9 (active) PA = 1.42 if PAL is estimated to be ≥ 1.9 < 2.5 (very active)	135.3 − (30.8 × age [y]) + PA × (10.0 × weight [kg] + 934 × height [m]) + 20 kcal Where PA is the physical activity coefficient: PA = 1.00 if PAL is estimated to be ≥ 1.0 < 1.4 (sedentary) PA = 1.16 if PAL is estimated to be ≥ 1.4 < 1.6 (low active) PA = 1.31 if PAL is estimated to be ≥ 1.6 < 1.9 (active) PA = 1.56 if PAL is estimated to be ≥ 1.9 < 2.5 (very active)
9-18 years	EER = 88.5 − (61.9 × age [y]) + PA × (26.7 × weight [kg] + 903 × height [m]) + 25 kcal Where PA is the physical activity coefficient: PA = 1.00 if PAL is estimated to be ≥ 1.0 < 1.4 (sedentary) PA = 1.13 if PAL is estimated to be ≥ 1.4 < 1.6 (low active) PA = 1.26 if PAL is estimated to be ≥ 1.6 < 1.9 (active) PA = 1.42 if PAL is estimated to be ≥ 1.9 < 2.5 (very active)	EER = 135.3 − (30.8 × age [y]) + PA × (10.0 × weight [kg] + 934 × height [m]) + 25 kcal Where PA is the physical activity coefficient: PA = 1.00 if PAL is estimated to be ≥ 1.0 < 1.4 (sedentary) PA = 1.16 if PAL is estimated to be ≥ 1.4 < 1.6 (low active) PA = 1.31 if PAL is estimated to be ≥ 1.6 < 1.9 (active) PA = 1.56 if PAL is estimated to be ≥ 1.9 < 2.5 (very active)

Step 2: For abnormal energy and nutrient intake values detected in Step 1, the corresponding Subject ID(s) and date(s) of intake will be used to examine both the "meal level" and "whole food level" data files. The DCC nutritionist(s) will notify the clinical site(s) of questionable meals and/or foods, and the site(s) is charge of fixing the data based on original food records and re-uploading the NDS backup files to the DCC with "rev" noted at the end of the filename. Every site is given 30 days from the date of notice to complete data correction. The DCC will re-calculate energy and nutrient intakes upon receiving the revised NDS files.

In addition, the DCC evaluates internal consistency by reviewing questions that should yield the same answer, such as participants' responses to questions about vitamin/mineral supplements, which is reported at two times during each TEDDY clinic visit -- in the TEDDY book and in the 3-day food record.

The DCC quality control review alerts the interviewers with possible data entry mistakes and offers potential ideas on probing for more detailed and accurate data.

.

12.10.2.3. Food frequency data of the mother

The food frequency data will be stored in the Oracle data system at the DCC. It is not possible to do the quality control of the food frequency data in a systematic way in centers. Individual questionnaires can still be re-checked in countries but the overall checking of the submitted data has to be carried out in the DCC. The DCC will look for errors like

- frequencies that are blank

- lines with several inconsistent frequencies (e.g. once a day and twice a week given)

- frequencies that are not feasible (e.g. fish soup 10 times a day regularly)

The DCC will document the detected errors and contact the respective sites regarding these. The mothers should be contacted and all the invalid values should be corrected and the respective FFQs with correct values re-submitted.

12.10.3. Biomarker analysis

Biomarkers of nutritional status are being collected in TEDDY in association with outcomes analysis. Both biomarker analysis and dietary intake analysis can provide information about diet at individual level but both of them have also limitations. It is important to keep in mind that these two general approaches of measuring exposure should be viewed as complementary, rather than one being a substitute or a confirmation for the other.

Biomarkers can also provide laboratory estimates of the validity of dietary intake that is reported in food recalls and diaries for nutrients of interest given that the limitations of the data are considered. Some of the biomarkers are short term, e.g. ascorbic acid, which would reflect only the previous day dietary exposure, some are medium term e.g. fat soluble vitamins, and some are longer term, e.g. the RBC membranes biomarkers would reflect about 6 weeks of exposure.

Nutrients of interest for validity estimation in TEDDY:

- Plasma alpha and gamma-tocopherols (biomarker of vitamin E intake)

- Erythrocyte fatty acid membrane composition (biomarker of omega-3 fatty acid intake)
- Plasma ascorbic acid

It is also important to consider how a biomarker is affected by laboratory procedures, so samples used for analysis of nutritional biomarkers will use laboratory quality control procedures that are outlined in Chapter 14 of the Manual of Operations.

12.11 Data Management

The TEDDY study relies on centralized data management whereby Clinical Centers, after local backup of dietary database files, transfer all records to the DCC. Data management for the TEDDY diet study involves site-specific, and DCC-specific operational procedures, as well as global procedures to ensure the privacy and confidentiality of collected diet-related data.

Privacy & Confidentiality of Data

Verbal data from the 24-hour recalls as well as the composite of written-verbal datasets from the 3-day food diaries are entered into a database at the Clinical Centers wherein the TEDDY subject is identified only by code – one code is issued by the DCC and another is a local code for the Clinical Center. Names, addresses and other personal information are not recorded in the databases, in keeping with considerations for privacy and confidentiality in all countries, and specifically with HIPAA requirements in the USA.

Site-Specific Data Management

Backup of the dietary interview is routinely conducted to ensure the security of the data. Daily back-up copies of the data are made to a computer diskette and stored in a location separate from the computer. At the end of each week, the last backup copy made of each interviewer's recalls will be given to the site lead nutrition person. Completed dietary recalls and food records should be archived at each site. An archived copy of all data should be kept until the study is complete.

The site lead nutrition person files copies of the all materials related to the dietary interview. The participant identification number will be used for record retrieval in the event of questions from the DCC or study investigators. The physical instruments from the 3-day food diaries are to be kept in the participant's file at the Clinical Centers.

Because of the differences in foods consumed among the four TEDDY countries – USA, Sweden, Finland and Germany -- each site uses a country-specific nutrient database to collect diet information. Detailed descriptions of each food database and data collections/entry/quality control procedures that are specific to these food databases are located in appendices to this section of the Manual of Operations. Food analysis databases in use for TEDDY are:

- Germany: LEBTAB, owned by Forschungsinstitut für Kinderernährung (Research Institute for Child Nutrition) (FKE)
- Sweden: Food database owned by the Swedish National Food Administration
- Finland: FINELI, owned by the National Public Health Institute

- United States: NDS-R, owned by the University of Minnesota, School of Public Health, and licensed to the TEDDY sites in the USA.

Data Transfer Overview

These current guidelines on data transfer are relevant to the nutrient data. The MOO will be updated later regarding the food level data. The Diet Committee and the diet sites are currently working on food level variables to be submitted to the DCC. The inter-country consistency of the information provided through these variables is being evaluated and the countries are taking actions to harmonize the data. Once this is done the detailed instructions regarding the data format and data transmission will be added to the MOO.

Each of the four TEDDY countries requires a different data transfer protocol, and the output files sent to the DCC have different formats and field names, depending on the country, due to differences in each country's nutrition database software. The processed food record data including header, energy and nutrient information will be provided per data entry row, i.e. per food or dish eaten, from the sites to the DCC. Once data is transferred to the DCC, the country-specific files are retained and stored, but the information is also uploaded to the centralized food record database (FRDB). In the FRDB the local variable names (header, energy and nutrients) are changed to generic which will be described in a separate data dictionary.

Naming the food record file

For all TEDDY dietary files sent to the DCC, the following naming scheme is used:
TD106_04NOV
Where:
TD= A constant (Teddy Diet)
106 = visit location code
(example 106 is TEDDY/DAISY Clinic in Colorado)
04 = year
NOV= month

The name of the food record file (File Name) should appear in every row within the file that is sent to the DCC (Table 1). It is required that the files include 11 header columns: **file name, subject ID, date of intake, meal time, visit location code, dietary data visit number, food ID, food description, food amount, date of entry, and staff ID**. The following headers are strongly recommended but not required: local code, meal site (e.g. home, at grandparents), meal type (e.g. breakfast, lunch), and description of day (e.g. normal, sick). Additional headers may be submitted but the DCC should be aware of the any extra variables. The current description of header columns from each country are given in Table 1. Any changes in it should be communicated with the DCC. Whenever the file is revised in the country and resent to the DCC the name should indicate the revision number in the file name by adding the _REV1 at the end. If multiple revisions then the _REV<#> at the end should indicate the version number: _REV2, _REV3, _REV4 etc.

Table 1. Column headers of food record files by country.

File Type	Column Header	Column Header Description
Finnish Dietary Data	IDENT	FIN Dietary File: Subject ID
Finnish Dietary Data	DAYDATE	FIN Dietary File: Dietary Data Date of Intake
Finnish Dietary Data	MEALTIME	Dietary Data Meal Time
Finnish Dietary Data	RECSITE	FIN Dietary File: Visit Location Code
Finnish Dietary Data	VISITNO	FIN Dietary File: Dietary Data Visit
Finnish Dietary Data	FOODID_TEDDY	FIN Dietary File: Dietary Data Food ID
Finnish Dietary Data	FOODNAME_TEDDY	FIN Dietary File: Dietary Data Food Description
Finnish Dietary Data	MASS	FIN Dietary File: Dietary Data Amount
Finnish Dietary Data	RECDATE	FIN Dietary File: Dietary Data Date of Entry
Finnish Dietary Data	DATAENTID	FIN Dietary File: Dietary Data Staff ID
Finnish Dietary Data	PROJECT	FIN Dietary File: File Name
Finnish Dietary Data	MEALTYPE	Dietary Data Meal Type
Finnish Dietary Data	DAYKIND	Dietary Data Day Kind
Finnish Dietary Data	MEALSITE	Dietary Data Meal Site
File Type	**Column Header**	**Column Header Description**
German Dietary Data	PARTICIPANT_ID	GER Dietary File: Subject ID
German Dietary Data	PARTICIPANT_NAME	GER Dietary File: Local Code
German Dietary Data	DATE_OF_INTAKE	GER Dietary File: Dietary Data Date of Intake
German Dietary Data	TIME	GER Dietary File: Meal Time
German Dietary Data	SITE_ID	GER Dietary File: Visit Location Code
German Dietary Data	VISIT_NUMBER	GER Dietary File: Dietary Data Visit
German Dietary Data	LMC	GER Dietary File: Dietary Data Food ID
German Dietary Data	DESCRIPTION	GER Dietary File: Dietary Data Food Description
German Dietary Data	PREP_WEIGHT	GER Dietary File: Dietary Data Amount
German Dietary Data	DATE_OF_ENTRY	GER Dietary File: Dietary Data Date of Entry
German Dietary Data	SITE	GER Dietary File: Meal Site
German Dietary Data	DATA_ENTRY_ID	GER Dietary File: Dietary Data Staff ID
German Dietary Data	PROJECT_NAME	GER Dietary File: File Name
German Dietary Data	PROJECT_ABBREVIATION	GER Dietary File: Site File Name
German Dietary Data	FPB	GER Dietary File: Food Portion Booklet
File Type	**Column Header**	**Column Header Description**
Swedish Dietary Data	DCCNR	SWE Dietary File: Subject ID
Swedish Dietary Data	TEDDYNR	SWE Dietary File: Local Code
Swedish Dietary Data	DATEINT	SWE Dietary File: Dietary Data Date of Intake
Swedish Dietary Data	KL	SWE Dietary File: Meal Time
Swedish Dietary Data	SITEID	SWE Dietary File: Visit Location Code
Swedish Dietary Data	DAG	SWE Dietary File: Dietary Data Visit
Swedish Dietary Data	LMK	SWE Dietary File: Dietary Data Food ID
Swedish Dietary Data	LIVSMEDEL	SWE Dietary File: Dietary Data Food Description
Swedish Dietary Data	MANGD	SWE Dietary File: Dietary Data Amount
Swedish Dietary Data	DATEENT	SWE Dietary File: Dietary Data Date of Entry

Swedish Dietary Data	DATAID	SWE Dietary File: Dietary Data Staff ID
Swedish Dietary Data	FILENAME	SWE Dietary File: File Name
Swedish Dietary Data	TYP	SWE Dietary File: Meal Type
Swedish Dietary Data	NOTES	SWE Dietary File: Day Kind
File Type	**Column Header**	**Column Header Description**
US Dietary Data	CPARTID	US Dietary File: Subject ID
US Dietary Data	CPNAME	US Dietary File: Local Code
US Dietary Data	DINTAKE	US Dietary File: Date of Intake
US Dietary Data	TMTIME	US Dietary File: Meal Time
US Dietary Data	CSITE	US Dietary File: Visit Location Code
US Dietary Data	CVISIT	US Dietary File: Visit
US Dietary Data	CNCCFDID	US Dietary File: Food ID
US Dietary Data	CFDNAME	US Dietary File: Food Description
US Dietary Data	RGRAMAMT	US Dietary File: Amount
US Dietary Data	DENTRY	US Dietary File: Date of Entry
US Dietary Data	IMPLACE	US Dietary File: Meal Site
US Dietary Data	CINTVW	US Dietary File: Staff ID
US Dietary Data	IAMOUNT	US Dietary File: IAmount
US Dietary Data	CTNOTE	US Dietary File: CTNote
US Dietary Data	IRELIABL	US Dietary File: IReliabl
US Dietary Data	CPROJECT	US Dietary File: File Name
US Dietary Data	CPJNAME	US Dietary File: Site File Name
US Dietary Data	IMNAME	US Dietary File: Meal Type

United States Data Transfer

TEDDY sites in the USA use the NDS-R database and associated software to collect dietary data. NDS-R is owned by the Nutrition Coordinating Center at the University of Minnesota College Of Public Health (NCC), and is licensed to the TEDDY project via the DCC. The DCC holds the master license for NDS-R, and one or more satellite licenses are allocated to Clinical Centers, depending on need. The Clinical Centers are authorized to use NDS-R solely for TEDDY records, and may not use the database or software in connection with other research, clinical, or other efforts. Clinical staff using NDS-R must be trained and certified by the NCC.

All of the NDS-R satellite licenses, and the master license, are “network authorized,” so they can operate as client-server applications within the local area networks at Clinical Centers. The licenses and support agreement documents are held at the DCC. User and technical documentation are provided to each satellite site, along with contact information to obtain technical support and troubleshooting assistance from the NCC. Local Clinical Center sites are responsible for software security and local backup, redundancy and disaster recovery procedures for their copies of the software. License agreements do not permit copies of the software to be made, but allow for copies to be made of the documentation for internal, noncommercial use.

To support centralized data management for TEDDY, each Clinical Center is required to create a database-specific back up file that is transmitted to the DCC as a zipped file

(standard *.zip* file extension). The backup file is a copy of one or more NDS-R data structures known as "Projects." Projects contain the completed dietary records that have been collected in connection with TEDDY. A backup file destination computer drive at the Clinical Centers is specified with the *User Preferences* tab of the *Preferences* window in NDS-R. And when the *Backup* utility is executed from the NDS-R menu, the software saves the Project(s) to the target destination, in the process creating zipped files with the file name(s) of the Project(s).

The backup zipped files are uploaded to the TEDDY web site at the DCC no later than the 25th of the month, using the procedure described below in the section "Upload of Dietary Data to the DCC." Additionally, following file transmission/upload, an email is sent to the DCC describing the file and its associated Project(s), including total number of Project(s) and total number of records within each Project, and information about the number of "missing" foods that may be included in the records (See the section below about missing foods.). The DCC sends an email to confirm receipt to the Clinical Center.

Once the backup files arrive at the DCC, the DCC will unzip the file and then execute the NDS-R *Restore* utility. When the backup file is "unzipped," each project is allocated to a distinct file on the destination computer drive, and the NDS-R *Restore* utility reads the targeted files and maps the Projects to the database associated with the DCC copy of NDS-R software.

Aggregate data from the Clinical Centers in the USA will initially be stored on the NDS-R system at the DCC, which is a client-server network application that is part of the computer configuration in place at the DCC, and is thus subject to the data storage, redundancy and disaster recovery requirements that apply to the entire TEDDY group of databases, programs and software applications. These DCC procedures are described in the Data Management section of the TEDDY Quality Control Document.

At specified intervals (monthly on or about the 30th of the month, after all monthly files have been reviewed and quality checked), the NDS-R data will be output to a SAS database at the DCC in preparation for subsequent analysis. Thus, there will be two storage sites for NDS-R dietary records at the DCC – one within the NDS-R data structure and one within SAS output file structure.

Software Updates, "New" and "Missing" Foods in NDS-R

On a quarterly basis, the NCC generates updates to the NDS-R database to include nutrient data for foods that are new to the marketplace. The quarterly updates are supplied in an NDS-R-specific data structure called a "User Recipe." As these updates are sent from the NCC, the DCC will forward them to Clinical Centers by loading them onto the TEDDY web site for local downloading.

There is often a "lag time" between the introduction of a food to the marketplace and its inclusion in NDS-R data files. The TEDDY project has considered this and will use the following procedure to resolve new, missing foods in NDS-R:

If a specific food is not found when the user clicks the *Search* or *Search All* buttons in NDS-R, the user will click the *User Recipe* radio button. This will cause NDS-R to display the files of new foods, as well as new foods that are already in place for TEDDY as user recipes.

The user searches for the product in the user recipe files. If the food is still missing after the food files are searched, the user tries to resolve the food using the data entry rules contained

in Appendix 15, and/or nutrient tolerances contained in Appendix 8 of the NDS-R User Guide

Data-entry rules are used after all probing techniques during the dietary recall have failed to elicit the required information, or after a search of foods reveals that the target food is not found in NDS-R. The purpose of the data entry rules and nutrient tolerances is to standardize the recording of reasonable equivalent foods or amounts that can be substituted in NDS-R. The table below contains the nutrient tolerances as adapted from recommendations in Appendix 8 of the NDS-R User Guide.

General Nutrient Tolerance Guidelines
(*Adapted for infants/toddlers from the NDS-R User Guide***)**

Nutrient	Per 100 grams product	Per 75 grams product	Per 50 grams product	Per 25 grams product	Per 10 grams product	Per 5 grams product
Calories	± 85.00 kcal	±64	±43	±14	±8	±0.5
Protein	± 5.00 gm	±3.75	±2.5	±1.25	±0.5	±0.25
Total fat	±2.50 gm	±1.9	±1.25	±0.63	±0.25	±0.13
Total carbohydrate	±10.00 gm	±7.5	±5	±2.5	±1	±0.5
Sodium	±100.00 mg	±75	±50	±25	±10	±5

Whenever data entry rules or product equivalents are used, it should be documented in the NDS-R *Notes* field for quality assurance purposes. In the *Notes* field, type a description of food with brand name (when available) and serving size, then save the record as usual. An effort should be made to obtain the nutrients and ingredient list from the product label. Study participants may be able to provide label information on foods eaten in their home.

If using the data entry rules and nutrient tolerances fails to yield a reasonable food or amount of food for TEDDY, then the item will be recorded as a "missing food." On a monthly basis, prior to transmission of backup NDS-R zip files to the DCC, the lead nutritionist at the Clinical Center will identify any missing foods and list them in the email report that accompanies data transmission to the DCC.

The DCC nutritionist will attempt to resolve the missing foods, either by obtaining information from the manufacturer, or submitting a "New Food Request" to NDS-R. When a new food is resolved by NDS-R, the DCC will create a new User Recipe file that is a .zip file, and distribute it to Clinical Centers via email or posting to the TEDDY website.

The lead nutritionist at Clinical Centers will use the NDS-R *Restore* utility to post the new food file to the database.

Annual Update of NDS-R Software

On an annual basis (typically June/July), the NCC issues a new release of the NDS-R database, which does not always include incorporation of the quarterly updated "User Recipes" into the main database. The updated version makes adjustments to delete foods that are no longer in the marketplace, and updates nutrient values in (numerous) cases where manufacturers have re-formulated their products. The TEDDY project must ascertain that

dietary records from NDS-R are properly associated with relevant dates of ingredients for marketplace foods. Otherwise there is risk of systemic error that could compromise the validity of data analysis. A specific timeframe and procedure for migrating from one version of NDS-R to the next is dependent on the timing of each software new release.

If the annual update of the NDS-R software follows the expected timeframe of late June release by the NCC, the migration procedure for TEDDY will occur as follows:

1. All TEDDY diet records for July will be entered and sent using the OLD NDS-R version.
2. TEDDY sites will install and prepare the new version of NDS-R for use to begin August 1st. All TEDDY diet records beginning August 1st will be entered using the new version.
3. During August, each site will complete double data entry for two children (six days worth of records) in both the old and new NDS version, and keep the Diet Committee informed of any (unexpected) adjustments to data entry or other procedures comparing the old and new version.
4. All user recipes developed for TEDDY by the DCC nutritionists will be restored to the updated version of NDS-R. Ingredient adjustments may need to be made based on the update.
5. Assuming no unforeseen problems, the NEW version will remain in place for one year (until the following July 31st, when a new update cycle will begin).
6. TEDDY Clinical Centers will retain the old version of NDS-R on computers or servers pending resolution of any "missing" foods, remembering that records must be updated or changed in the version of NDS in which they originated. All diet records can be VIEWED from old versions, but cannot be CHANGED.

Dietary Supplement Assessment Module

The NDS-R 2007 version features a dietary supplement assessment module known as DSAM. With the addition of DSAM, the NDSR software now links to two separate databases, the NCC Food and Nutrient Database and the DSAM database, and NCC enhanced version of the National Health and Nutrition Examination Survey (NHANES) Dietary Supplement Database 2003-2004. TEDDY implemented this module into the diet record collection on November 1, 2007.

Since the DSAM-NHANES Database includes only dietary supplements and antacids reported during the 2003-2004 NHANES data collection period, the NCC has enhanced the database by including a comprehensive ingredient file that facilitates the addition of DSAM User Products when "missing" dietary supplements are reported and cannot be found in the DSAM database. A DSAM user product is a record type that allows for a description of ingredients and the quantity of the ingredients to be entered to create a new dietary product. The DSAM user product can then be added to the DSAM database utilized by TEDDY.

Colorado site will create DSAM projects for locally reported new supplements. Other US sites will email or fax the DCC with the nutrition labels of new DSAM request. See Chapter 7: Managing DSAM User-Product Records in the NDS-R 2007 Manual. The user-product project is titled in the format of "Vitamins from (THE SITE) DDMONYR". For example,

Vitamins from Denver_25NOV07. New DSAM files are to be uploaded to the DCC website as soon as possible in order for all sites to enter new supplements.

Each DSAM user-product record will be identified by a unique Product ID; no record should have the same Product ID. When a new user-product record is developed at the site, the Product ID will be assigned based on the site ID starting with 001. For example, Denver product IDs will be assigned as 106_001, 106_002, etc., where "106" stands for the TEDDY/DAISY Clinic in Colorado. ***The DSAM user products will be entered in regular font in order to differentiate the TEDDY specific products from the DSAM products, which are in upper case.***

US file Naming Schema

For US sites, the zip files generated by NDS-R need to be renamed at the time of creation accordingly. For sites that need to send multiple files each month, the designation _1 or _2 is to be added to the name (i.e. TD106_04NOV_1). For any revised files, due to new foods or other file modifications at the clinical sites the designation _REV# is to be added to the name (i.e. TD106_04NOV_REV1). This will indicate to the DCC that this file was previously received and has been revised.

European Sites Data Transfer

Germany

On a monthly basis, the lead nutrition person for TEDDY in Dortmund, Germany makes a SAS dataset from LEBTAB. Only complete records are entered into the database. Each record includes a "header" with field identifiers shown in Table1. The SAS files are transmitted to the DCC via procedure described below in the section "Upload of Dietary Data to the DCC." Data transfer schedules are similar to those described above for US sites. However, due to country-specific computer operational requirements, Germany sends data transmissions no later than the 25th of the month.

Following file transmission/upload, the lead nutrition person in Germany sends an email to the DCC describing the file and its associated records, including total number of records. The DCC sends an email to confirm receipt to the Clinical Center.

There are two storage sites for German dietary records at the DCC – one within the Excel structure kept by the DCC nutritionist, and the other within a SAS output file structure that will be used for subsequent data analysis. Only one SAS file is stored.

Software Updates, New and "Missing" Foods

All dietary records have to be checked after arrival in Dortmund for food products that are not included in the database. Missing non-processed and processed food items are added by the nutritionist in the database.

For commercial products, information is requested from the parents for the name of the producer and brand name. The family is advised to send cartons/wrappers etc. of every commercial product to ensure that ingredients, data on fortification and the "best before date" are available. If information is missing on the carton (e.g. mostly the producer does not give details on what kind of oil was used), the manufacturer will be contacted. The nutritionist then follows up with food companies and adds new/changed product data to the database.

Two new products are added to the database, on average, every week. The dietitian adds new commercial products consumed by study participants and not currently in the database, into LEBTAB via a recipe which is simulated from the ingredients listed on the label and controlled by those nutrient contents declared by the manufacturer. To get up-to-date information on ingredients, it is necessary that all dietary records are checked in "real time" for new products, which are not currently in the database, rather than at the end of the study when less information is available.

In the nutrient database the FKE monitors changes in the supply of commercial food products (e. g. due to fortification) continuously. A new product (e. g. due to a modified recipe or new ingredients) is entered with a new food code into the nutrient database, which the synchronization between food records and concurrent food market, which is a specific necessity for the analysis of longitudinal data.

Finland

To support centralized data management for TEDDY, the Clinical Center in Finland will create a database-specific back up file from FINELI that is transmitted to the DCC. The backup files are sent to the DCC no later than the 25th of the month, using the procedure described below in the section "Upload of Dietary Data to the DCC." Additionally, following file transmission/upload, the Clinical Center sends an email to the DCC describing the file, including total number of records, and information about the number of "missing" foods that may be included in the records. The DCC sends an email to confirm receipt to the Clinical Center.

Each FINELI record for TEDDY will include a "header" with these field identifiers, shown in Table 1.

Software Updates, New and "Missing" Foods

The study nurses check all the food records at Clinical Centers during the visits of the family. In addition, nutritionists check the food records at National Public Health Institute, Helsinki e.g., for new food items and supplements.

The families are asked to report the brand names and manufacturers of all commercial products. The product information is collected from the manufacturers and from the Internet. The Fineli baby food database is updated once or twice a year by a nutritionist. In addition, all other new food items are added to the Fineli database once or twice a year by the nutritionist. The changes in new commercial baby foods, their nutrient contents and recipes of commercial foods are monitored twice a year and updated to the database accordingly. In addition, other foods are monitored and updated likewise.

The Finessi software enables the nutritionists to modify the recipes of foods to be equivalent to the actual recipes of foods that the child has eaten. In addition, the modification of recipes can be used to enter some commercial foods accurately, e.g. bread, commercial meals etc.

All the foods, including commercial baby foods, are filed in the database according to the year of the data collection. This enables monitoring of the diet accurately in a longitudinal study.

Sweden

To support centralized data management for TEDDY, the Clinical Center in Sweden will create a database-specific back up file from the Swedish National Database that is transmitted to the DCC. The backup files are sent to the DCC no later than the 25th of the month, using the procedure described below in the section "Upload of Dietary Data to the DCC." Additionally, following file transmission/upload, the Clinical Center sends an email to the DCC describing the file and total number of records. The DCC sends an email to confirm receipt to the Clinical Center.

Each record from Sweden for TEDDY will include a "header" with these field identifiers, shown in Table 1.

Table 2: Visit Number Naming Conventions for 24 hour recall and 3 day diet records data submission to the DCC

Visit Number:	US, Finland and Germany use:	Sweden uses:
3 month visit – 24 hour recall	1Z	13
6 month	2a (first day); 2b (second day); 2c (third day)	16 (first day); 26 (second day); 36 (third day)
9 month	3a (first day); 3b (second day); 3c (third day)	19 (first day); 29 (second day); 39 (third day)
12 month	4a (first day); 4b (second day); 4c (third day)	112 (first day); 212 (second day); 312 (third day)
18 month	5a (first day); 5b (second day); 5c (third day)	118 (first day); 218 (second day); 318 (third day)
24 month	6a (first day); 6b (second day); 6c (third day)	124 (first day); 224 (second day); 324 (third day)
30 month	7a (first day); 7b (second day); 7c (third day)	130 (first day); 230 (second day); 330 (third day)
36 month	8a (first day); 8b (second day); 8c (third day)	136 (first day); 236 (second day); 336 (third day)
42 month	9a (first day); 9b (second day); 9c (third day)	142 (first day); 242 (second day); 342 (third day)
48 month	10a (first day); 10b (second day); 10c (third day)	148 (first day); 248 (second day); 348 (third day)
4.5 years	11a (first day); 11b (second day); 11c (third day)	154 (first day); 254 (second day); 354 (third day)
5 years	12a (first day); 12b (second day); 12c (third day)	160 (first day); 260 (second day); 360 (third day)

Visit Number:	US, Finland and Germany use:	Sweden uses:
5.5 years	13a (first day); 13b (second day); 13c (third day)	166 (first day); 266 (second day); 366 (third day)
6 years	14a (first day); 14b (second day); 14c (third day)	172 (first day); 272 (second day); 372 (third day)
6.5 years	15a (first day); 15b (second day); 15c (third day)	178 (first day); 278 (second day); 378 (third day)
7 years	16a (first day); 16b (second day); 16c (third day)	184 (first day); 284 (second day); 384 (third day)
7.5 years	17a (first day); 17b (second day); 1c (third day)	190 (first day); 290 (second day); 390 (third day)
8 years	18a (first day); 18b (second day); 18c (third day)	196 (first day); 296 (second day); 396 (third day)
8.5 years	19a (first day); 19b (second day); 19c (third day)	1102 (first day); 2102 (second day); 3102 (third day)
9 years	20a (first day); 20b (second day); 20c (third day)	1108 (first day); 2108 (second day); 3108 (third day)
9.5 years	21a (first day); 21b (second day); 21c (third day)	1114 (first day); 2114 (second day); 3114 (third day)
10 years	22a (first day); 22b (second day); 22c (third day)	1120 (first day); 2120 (second day); 3120 (third day)
10.5 years	23a (first day); 23b (second day); 23c (third day)	1126 (first day); 2126 (second day); 3126 (third day)
11 years	24a (first day); 24b (second day); 24c (third day)	1132 (first day); 2132 (second day); 3132 (third day)
11.5 years	25a (first day); 25b (second day); 25c (third day)	1138 (first day); 2138 (second day); 3138 (third day)
12 years	26a (first day); 26b (second day); 26c (third day)	1144 (first day); 2144 (second day); 3144 (third day)
12.5 years	27a (first day); 27b (second day); 27c (third day)	1150 (first day); 2150 (second day); 3150 (third

Visit Number:	US, Finland and Germany use:	Sweden uses:
		day)
13 years	28a (first day); 28b (second day); 28c (third day)	1156 (first day); 2156 (second day); 3156 (third day)
13.5 years	29a (first day); 29b (second day); 29c (third day)	1162 (first day); 2162 (second day); 3162 (third day)
14 years	30a (first day); 30b (second day); 30c (third day)	1168 (first day); 2168 (second day); 3168 (third day)
14.5 years	31a (first day); 31b (second day); 31c (third day)	1174 (first day); 2174 (second day); 3174 (third day)
15 years	32a (first day); 32b (second day); 32c (third day)	1180 (first day); 2180 (second day); 3180 (third day)

All TEDDY diet record files should be sent as .CSV, .xls, or .sas7bdat, except for files from the USA, where the obligatory file extension .zip is generated by NDS-R. If the files are sent in these formats then the DCC will be able to process European method of recording dates and the use of commas, "," instead of decimal points, "." in the decimal values.

Upload of Dietary Data to the DCC

Clinical sites use the following procedure to send data to the DCC.

1. Log in to the TEDDY website.
2. Click on 'Data Upload' under the 'Data Management' heading of the left navigation menu.
3. To upload the dietary data files from your database, click the 'Browse…' button on the data upload page. This will give you a standard windows type explorer so you can find the files you wish to submit. Once you have found the file, click 'Open'.
4. Click 'Upload' to send the selected file to the DCC.
5. Once your submission is final you will see the name, upload status, and upload date/time of your file in the recent uploaded files list on this page.
6. The "Data Upload" program also transmits an email to notify the DCC that file upload has occurred. This email is in addition to the email that each clinical site sends to describe the records in the file.

Comparison of the Food Databases

Given that the dietary data of each country need to be entered and calculated locally using national or local food databases, the different food databases used in TEDDY need to be carefully compared. A comparison of the Food Databases is included in Appendix 12.2.

Dietary Supplement Data Management

The TEDDY study acknowledges that nutrient databases are limited in capturing all marketed dietary supplements at any time. The diet committee, therefore, explicitly documents every dietary supplement consumed by the study participants and their parents with the purpose of creating a most comprehensive dietary supplement database to compliment the nutrient databases currently employed in the study. Maternal consumption of dietary supplements is collected using the First TEDDY Study Questionnaire For the Mother, and the use among infants and children are reported in the TEDDY books. Acknowledging the dietary supplement market constantly changes and the remarkable variations among TEDDY countries, the Diet Committee implements the following categories when coding dietary supplements.

1) The codes for adult single vitamin supplements consist of an "S" and a 4-digit number, with the exception of Finnish codes being a 5-digit number without "S". These 5-digit codes are pre-designated in the Finnish database.
2) Adult multivitamin supplements are coded with the letter "M" and a 4-digit number. The codes are assigned based on brand name and specific type.
3) Infant/child multivitamin supplements are assigned with codes consisting of the letter "B" and a 4-digit number. These supplements are coded by brand names and specific type, and may be either single vitamin or multivitamin.
4) Adult supplements may be consumed by infants/children, which is relatively more common in Finland and Sweden. The diet committee, in such cases, assigns a "B" code based on the brand name and specific type. This has recently been adopted by the U.S. sites as well.
5) Different from the European market, the U.S. companies produce a category of multivitamin supplements as prenatal supplements to help pregnant women achieve optimal nutritional status, particularly the needs for folic acid and iron during pregnancy . All prenatal supplements are coded with the letter "P" and a 4-digit number based on the brand names and specific type.
6) The TEDDY study does NOT code pure herbal or pure homeopathic supplements as dietary supplements. However, it is important to thoroughly examine the ingredient list of every dietary supplement in that some plant-based products or homeopathic products may be fortified with vitamins and/or minerals and/or probiotics, and, therefore, need to be coded as dietary supplements. Sites should review the complete ingredient list of the product before classifying it as purely herbal or purely homeopathic. If the product contains added vitamins, minerals probiotics, etc then it should be coded in the dietary supplements section. If the product is deemed to be purely herbal or purely homeopathic, which means that it does not contain any added vitamins, minerals, probiotics, etc, and it is taken for a medical condition then it

should be coded under the medications section. See MOO sections 10 and 11 for further details.

7) According to the coding rules established by the Clinical Committee, any product containing medically active ingredients that is given for a medical condition will be coded as medication and only the medically active ingredients are listed in the code details. In some instances, medications contain additional nutrient(s) and/or nutrition component such as flu medications is fortified with ascorbic acid. Such products will be coded as medications, however the added nutrients will not be displayed in the code details. Products used to treat medical conditions will be coded as dietary supplements if only vitamins and/or minerals are the functional ingredients. Examples include Tums and Rolaids. Any given product will receive one code only, either a supplement code or a medication code.
8) Vitamin K injections administered to newborn infants are not to be coded.

Every U.S. clinic and European country is in charge of identifying an appropriate code for every supplement. If there is no corresponding existing code, the clinic will request a new code from the DCC with product information (copy of the label preferred) included in the request. Again, the exception would be Finland where codes are pre-assigned in the database. The Finnish researchers inform the DCC every time a code is assigned to a supplement.

All clinics are expected to indicate which subgroup a supplement falls into when requesting for a supplement code, which simplifies the searching process using the TEDDY codebook online and subsequent data analysis. Below is the summary of supplement subgroups. Every supplement should be assigned to one subgroup.

Subgroups for single and multivitamin/mineral supplements

a. Proposed subgroups for single supplements:
   1 Vitamin D
   2 Vitamin C
   3 Probiotic
   4 Single Fatty Acid (e.g. DHA, EPA, GLA, DGLA, AA)
   5 Calcium
   6 Vitamin B6
   7 Vitamin B12
   8 Folic Acid
   9 Vitamin A
   10 Vitamin E
   11 Iron
   12 Niacin
   13 Zinc
   14 Magnesium
   15 Potassium
   16 Choline
   17 Vitamin B1
   18 Vitamin B2
   19 Biotin

20 Pantothenic Acid
21 Selenium
22 Chromium
23 Fluorine
24 Betacarotene
25 Iodine
26 Copper
27 Antioxidants (non-vitamin/mineral) (e.g. lycopene, coenzyme Q10, melatonin)

b. Proposed subgroups for multivitamin/mineral supplements:
1 Multivitamins/minerals with probiotic (no vitamin D, no fish oil/fatty acids (FAs))
2 Multivitamins/minerals containing vitamin D (no probiotic, no fish oil/FAs)
3 Multivitamins/minerals (no vitamin D, no probiotic, no fish oil/FAs)
4 Multivitamins/minerals with fish oil/FAs (no vitamin D, no probiotic)
5 Multivitamins/minerals with fish oil/FAs containing vitamin D (no probiotic)
6 Multivitamins/minerals with probiotic and fish oil/FAs and containing vitamin D
7 Multivitamins/minerals with probiotic containing vitamin D (no fish oil/FAs)
8 Multivitamins/minerals with probiotic and fish oil/FAs (no vitamin D)
9 Antioxidants (products with several non-vitamin/mineral antioxidants, e.g. combination of lycopene, coenzyme Q10, melatonin etc)
10 Mixture of FAs without vitamin/mineral (no probiotic, no vitamin D)

The table below also illustrates the grouping structure of multivitamin/mineral supplements

Vitamin D +	**Group**	**Vitamin D -**	**Group**
Fish oil/FAs +		Fish oil/FAs +	
Probiotic +	B6	Probiotic +	B8
Probiotic –	B5	Probiotic –	B4
Fish oil/FAs –		Fish oil/FAs –	
Probiotic +	B7	Probiotic +	B1
Probiotic -	B2	Probiotic -	B3

Non-vitamin/mineral antioxidants B9

E.g. combination of selenium, coenzyme Q10, melatonin, etc.

Section 12 Appendix

A. **3-day Food Record Forms with Instructions (Finland, Germany, Sweden, and US, in Finnish, German, Swedish, and English)**
B. **Day Care Food Intake Forms (Sweden and US, in Swedish and English)**
C. **24-hour Recall and Food Interviewer Assessment Form**
D. **Description of the Nutrient Databases**
E. **Comparison of Nutrient Databases**

A. 3-Day Food Record Forms\
Finland (in Finnish and English)

Olkaa ystävällinen ja ottakaa tämä lomake ja lapsenne Teddy-kirja seuraavalle käynnille!

TEDDY –tutkimus

Tutkittavan koodi:

Paikalliskoodi:

6 KK IKÄISEN LAPSEN RAVITSEMUS

Tutkimushoitaja täyttää
Lapsen nimi _____

Lapsen syntymäaika |__|__|__|__| 20 |__|__|
p p k k v v

Lapsen sukupuoli 1. poika 2. tyttö

Lomakkeen vastaanottaja _____

Vastaanottopäivä |__|__|__|__| 20 |__|__|
p p k k v v

Lomake vastaanotettu 1. henkilökohtaisesti
2. postitse
3. muulla tavoin, miten _____

Lomake on tarkistettu ja tarvittaessa täydennetty 1. kyllä
2. ei, syy _____

Lomake on tarkistettu 1. käynnillä
2. puhelimessa

HYVÄT VANHEMMAT!

Tässä tutkimuksessa selvitetään lapsen ravitsemusta. Pyydämme teitä merkitsemään kaikki lapsenne nauttimat ruoat ja juomat seuraavan kolmen päivän ajalta:

|__|__|__|__|; |__|__|__|__|; |__|__|__|__| 20 |__|__|
p p k k p p k k p p k k v v

Mikäli ruokapäiväkirjan täyttäminen ei onnistu yllä mainittuina päivinä, voitte vaihtaa päivät niten, että mukaan tulee 2 arkipäivää ja 1 viikonlopun päivä. Jos teillä on kysyttävää tutkimuksesta tai lomakkeen täyttämisestä, ottakaa yhteyttä _____. Kiitos osallistumisesta tutkimukseen.

Kysymyksiin vastaajan nimi _____
Osoite _____
_____puh. ____/_____
Vastaaja on lapsen 1. äiti
2. isä
3. muu, kuka _____

Vastauspäivä |__|__|__|__| 20 |__|__|
p p k k v v

Please, take this questionnaire and your child's TEDDY book to the next visit!

TEDDY study

Code:

CHILD'S DIET AT THE AGE OF 6 MONTHS

Research nurse completes
Child's name _____

Child's date of birth |__|__|__|__| 20 |__|__|
d d m m y y

Filled food diary received by_____

Date of receival |__|__|__|__| 20 |__|__|
d d m m y y

Food diary received 1. personally
2. by mail
3. in an another way, how_____

Food diary checked and if necessary completed 1. yes
2. no, why_____

Food diary checked 1. at the visit
2. by telephone

DEAR PARENTS!

In this study the diet of children is being investigated. We ask you to write down everything your child eats during the following 3 days:

|__|__|__|__|; |__|__|__|__|; |__|__|__|__| 20 |__|__|
d d m m d d m m d d m m y y

If it is not possible to keep the food diary on these given days you can change the days choosing three days which include 1 day in the weekend. Should you have any questions about the study or about this questionnaire please, contact _____. Thank you for participating in this study.

Name of the responder _____
Address _____
_____phone ____/_____
The responder is the child's 1. mother
2. father
3. somebody else, who_____

Date |__|__|__|__| 20 |__|__|
d d m m y y

PÄIVÄMÄÄRÄ I_1I_5I_0I_9I 20 I_0I_6 VIIKONPÄIVÄ ___Perjantai___

Aika ja paikka	Ruoat ja juomat	Kauppanimi tai valmistusaineet Valmistustapa	Syöty/juotu määrä
3.30 koti	Imetys		
8.00 koti	Imetys		
	Kauravelli PLUS	Nutricia Muksu (5-6 kk)	1 dl
10.30 koti	Äidinmaidonkorvike	Tutteli Plus 1 (0-6 kk), nestemäinen	70 ml
	Peruna-porkkana-kukkakaalisoss	Peruna (1/2), porkkana (1/4) ja kukkakaali (1/4) keitetty vedessä, soseutettu, nesteenä Tutteli Plus 1 (0-6 kk) nestemäinen, ei lisätty suolaa	3 rkl
	Broileri	Keitetty, ei lisätty suolaa	1 tl
13.00 koti	Imetys		
	D-vitamiinivalmiste	Jekovit	3 tippaa
	Vesijohtovesi		1 ruokalusikka (rkl)
	Mangoa soseena	Semper (>4 kk)	3 tl
16.30 koti	Imetys		
17.00 koti	Imetys		
19.00 isovanhemmilla	Äidinmaidonkorvike	Nestlé Nan 1, jauheesta, pakkauksen ohjeen mukaan	1,5 dl
	Mustikkaa	1 dl tuoreita mustikoita, ½ tl sokeria, soseutettu	2 tl
22.00 koti	Imetys		

MUISTA MERKITÄ NÄMÄ!
* Lisätty sokeria tai suolaa?
* Rasvaa leivällä?

* Vesi- vai maitopohjainen?
- Puuro, velli
- Kastike
- Perunasose
- Kasvissose

*Millainen?
* Kauppanimi
- Maito
- Rasva
- Liha
- Makkara
- Juusto
- Leipä

* Valmistusaineet?
- Maito/vesi
- Rasva
- Jauhot

DATE I_2I_5_0I_5I 20 I_0I_7I WEEKDAY ___Friday___

Time and place	Foods and drinks	Brand name or ingredients Preparation of the food	Amount eaten/drunk
3.30 home	Breastfeeding		
8.00 home	Breastfeeding		
	Oat gruel Plus	Nutricia Muksu (5-6 months)	1 dl
10.30 home	Breastfeeding		
	Mashed potato	Boiled potato 2/3, Nutricia Tutteli Plus 2 (6-12 months) liquid infant formula 1/3	3 tbs
	Chicken	Boiled, no added salt	1 tsp
13.00 home	Breastfeeding		
	Vitamin D supplement	Jekovit	3 drops
	Tap water		1 tablespoon (tbs)
	Mangopure	Semper (4 months)	3 tsp
15.30 home	Breastfeeding		
17.00 home	Breastfeeding		
19.00 at grandparents	Infant formula	Nutricia Tutteli Plus 2 (6-12 months), liquid	1,5 dl
	Blueberries	Mashed, a quarter of tsp added sugar	2 tsp

REMEMBER TO REPORT THESE!
* Added sugar or salt?
* Fat on bread?

* Water or milk based?
- Cooked cereals
- Sauce
- Mashed potatoes
- Mashed vegetables

*What kind of?
* Brand name?
- Milk
- Fat
- Meat
- Sausage
- Cheese
- Bread

* Ingredients?
- Milk/water
- Fat
- Flour

PÄIVÄMÄÄRÄ p p k k v v |_|_|_|_|_| 20 |_|_| VIIKONPÄIVÄ _____

Aika ja paikka	Ruoat ja juomat	Kauppanimi tai valmistusaineet Valmistustapa	Syöty/juotu määrä

MUISTA MERKITÄ NÄMÄ!
* Lisätty sokeria tai suolaa?
* Rasvaa leivällä?

* Vesi- vai maitopohjainen?
- Puuro, velli
- Kastike
- Perunasose
- Kasvissose

*Millainen?
* Kauppanimi?
- Maito
- Rasva
- Liha
- Makkara
- Juusto
- Leipä

* Valmistusaineet?
- Maito/vesi
- Rasva
- Jauhot

5

DATE |_|_|_|_|_|20|_|_| WEEKDAY _____
d d m m y y

Time and place	Foods and drinks	Brand name or ingredients Preparation of the food	Amount eaten/drunk

REMEMBER TO REPORT THESE!
* Added sugar or salt?
* Fat on bread?

* Water or milk based?
- Cooked cereals
- Sauce
- Mashed potatoes
- Mashed vegetables

*What kind of?
* Brand name?
- Milk
- Fat
- Meat
- Sausage
- Cheese
- Bread

* Ingredients?
- Milk/water
- Fat
- Flour

Germany (in German and English)

TEDDY Studie

3-Tages Ernährungsprotokoll

Subject ID: _ _ _ _ _ _

Local Code: _ _ _ _ _

Bitte führen Sie das Ernährungsprotokoll Ihres Kindes während der folgenden drei Tage:

Tag, Datum ________ Tag, Datum ________ Tag, Datum ________

Falls Sie an einem oder mehreren dieser Tage kein Protokoll führen können, wählen Sie bitte zwei Wochentage und einen Wochenendtag innerhalb des Zeitraumes von 1 Woche vor oder nach dem Termin der Blutabnahme.

1. Tag: Datum: ____________ Wochentag: _______________

   Dieser Tag wurde protokolliert von:

   [ ] Mutter [ ] Vater [ ] andere: _____________

   Kinderbetreuung*: [ ] Nein [ ] Ja**

2. Tag: Datum: ____________ Wochentag: _______________

   Dieser Tag wurde protokolliert von:

   [ ] Mutter [ ] Vater [ ] andere: _____________

   Kinderbetreuung*: [ ] Nein [ ] Ja**

3. Tag: Datum: ____________ Wochentag: _______________

   Dieser Tag wurde protokolliert von:

   [ ] Mutter [ ] Vater [ ] andere: _____________

   Kinderbetreuung*: [ ] Nein [ ] Ja**

Bitte senden Sie uns das 3-Tages Ernährungsprotokoll zu, oder bringen Sie es bei Ihrem Institutsbesuch mit.

Beim Kinderarzt / im Studiencenter:

Gewicht: ______ kg Größe: ______cm Messdatum: __________

* Betreuung bei Ihnen zu Hause oder zu Hause bei jemand anderem: Tagesmutter, Kindertagesstätte, Kindergarten, Kinderhort, Vorschule.
** Falls Ja, bitte verwenden Sie den Zusatzbogen „Ernährungsprotokoll bei Kinderbetreuung".

Tag Nr. ___

Bitte geben Sie die Namen der verzehrten Lebensmittel, Getränke und der ggf. eingenommenen Medikamente möglichst genau an. Wir benötigen auch Angaben z. B. zum Fettgehalt (Milch, Käse, Wurst) oder zum Fruchtgehalt (Saft, Nektar) sowie Zusätze von Vitaminen.

Bitte bewahren Sie die Verpackung der Produkte auf und schicken Sie sie mit!

Wann? Uhrzeit	Wo? Ort*	Was? Gefäß/+Lebensmittel bzw. Getränk; Nährstoffpräparate, Medikamente	Wie viel? g	Rest g

* Betreuung bei Ihnen zu Hause oder zu Hause bei jemand anderem: Tagesmutter, Kindertagesstätte, Kindergarten, Kinderhort, Vorschule.
** Falls Ja, bitte verwenden Sie den Zusatzbogen „Ernährungsprotokoll bei Kinderbetreuung".

TEDDY Study
3-day diet record

Subject ID: _ _ _ _ _ _ Local Code: _ _ _ _ _ _

Please keep the record of your child during following 3 days:

_____ Day of the week, date _____ Day of the week, date _____ Day of the week, date

If it is not possible to keep the food record on one or more of these days please record 2 weekdays and 1 weekend day, during one week before or after the date of the blood sampling.

1. Day: date: _____ weekday: _____
   This day was recorded by:
   [ ] mother [ ] father [ ] other: _____
   daycare*: [ ] no [ ] yes**

2. Day: date: _____ weekday: _____
   This day was recorded by:
   [ ] mother [ ] father [ ] other: _____
   daycare*: [ ] no [ ] yes**

3. Day: date: _____ weekday: _____
   This day was recorded by:
   [ ] mother [ ] father [ ] other: _____
   daycare*: [ ] no [ ] yes**

Please send us the 3 day food record or hand it over at your clinic visit.

At the pediatrician / at the clinic:
weight: _____ kg length: _____cm date of measurement: _____

* Day care in your home or outside your home: daymother, day-care center, kindergarten, pre-school.
** If „Yes" please use the extra from „day record at day care".

Day nr. ___

Please write down all foods, beverages, medications or dietary supplements and describe them as accurately as possible. We need information e.g. about the fat content (milk, cheese, cold meat) or about the fruit content (juice, nectar) as well as fortified vitamins.

Please keep the packages of the foods and send them in with the record!

When? Time	Where? place*	What? container/+ food or beverages; vitamin/mineral preparations, medications	How much prepared ? g	Left over g

Sweden (in Swedish and English)

MATDAGBOK

Barnets namn ..... Local code .....

Vilken veckodag registreras barnets mat (ringa in)?

mån tis ons tors fre lör sön Datum .....

Om det behövs så använd flera blad. Börja varje ny dag på ny sida!

Detta är sidan ..... av ..... sidor.

När åt eller drack barnet?	Beskriv vad barnet åt och drack. Ange tillagningssätt (stekt, kokt), fett vid stekning, märke på halvhelfabrikat samt salt.	Var åt barnet? (hemma/restaurang)	Hur mycket fick barnet?	Hur mycket åt barnet?

Fick barnet något kosttillskott (tex. AD-droppar) under dagen?

FOOD RECORD

The Childs name ..... Local code .....

What day of the week is covered in the food record (circle one)?

mon tue wed thu fri sun sat Date .....

If needed, use more pages. Start each day on a new page!

This is page ..... of ..... pages.

What time did your child eat or drink?	Describe what the child ate or drank. Report cooking method (fried, boiled), fat used when frying, brand names and if salt is used etc.	Where did the child eat? (home or restaurant)	How much did your child get (at the plate)?	How much did your child eat?

Did the child get any dietary supplements (e.g. AD-drops) during the day?

US

DEAR PARENTS,
In this study, the diet of children is being studied.
We ask that you write down everything your child eats on the following 3 days:

_____
_____
_____

ID _____
TC _____
DOB _____
AGE_____
MALE / FEMALE

If it is not possible to keep the diet record on the given days, you can change the days choosing three days which include **one day of the weekend, and two weekdays**. The diet record should be done during three days that are within one week of your visit to the TEDDY clinic.

Should you have any questions about the study or about the food record, please contact the TEDDY Study Staff at 303.724.7577.

Thank you for participating in this study!

Name of the person completing form: _____

Phone: _____ / _____

Clinic Staff to Complete:

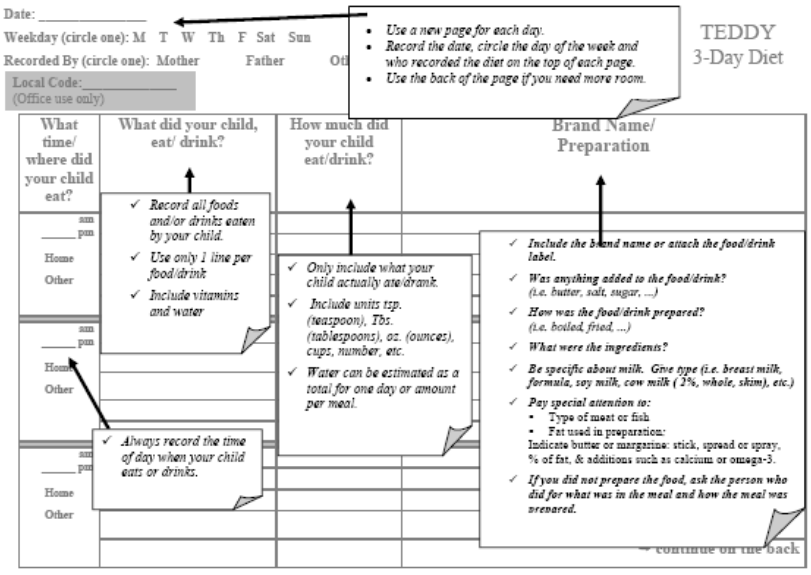
Child's name: _____

Diet record checked 1. At the visit 2. By telephone

Diet record received by: _____ Date of receipt: _____/ _____ 20 ____

Diet record received: 1. In person 2. By mail 3. Other _____

Age in Months	6 M	9m	12m	18m	24m	30m	36m	42m	48m	54m	60m	66m	72m
Visit #	2	3	4	5	6	7	8	9	10	11	12	13	14



Date: 10-29-2004
Weekday (circle one): M T W Th (F) Sat Sun
Recorded By (circle one): (Mother) Father Other_____
Local Code: _____ (Office use only)

TEDDY
3-Day Diet

EXAMPLE 1

What time/ where did your child eat?	What did your child, eat/ drink? • Use 1 line per food/drink • Include vitamins and water	How much did your child eat/drink? • Include units (oz., tbs., tsp., cups, etc.)	Brand Name/ Preparation • Was anything added? • How was the food/drink prepared? • If the food was prepared, what were the ingredients? • Milk: indicate if breast milk, formula, cow's milk, etc.
(am) 6:00 pm (Home) Other	Breast milk		From breast
(am) 8:00 pm (Home) Other	Rice cereal	1 Tbs.	Del Monte rice cereal made with 5 Tbs. Enfamil w/ Iron liquid formula.
	Potatoes	2 tbs.	Red potato, boiled in water and mashed
	Pears	1/2 jar	Del Monte Nature's Goodness Stage 2 Pears 4 oz. jar
	Vitamin Drops	1.0 ml	Poly Vi Sol 0.25 mg mixed in cereal
(am) 10:00 pm Home (Other)	Cheerios	1/2 cup	Dry cereal, no milk
	Apple Juice	3 fluid oz	Beech-Nut Apple Juice, From bottle
			↪ continue on the back

EXAMPLE 1 (continued)

What time/ where did your child eat?	What did your child, eat/ drink?	How much did your child eat/drink?	Brand Name/ Preparation
am 12:00 (pm) (Home) Other	Chicken Noodle Dinner	1 jar	Gerber stage 3 Chicken Noodle Dinner 4 oz. jar
	Green Beans and Potatoes	1 jar	Gerber Tender Harvest-stage 2, 4 oz. jar
	Tap water	2 fluid oz	Sipped from cup with meal
	Formula	4 fluid oz	Enfamil w/ iron powder mixed w/ tap water
am 3:30 (pm) (Home) Other	Banana	3 tsp.	Fresh, Mashed
	Breast milk		From breast
am _____ pm Home Other			
am _____ pm Home Other			

Date: 10-29-2004

Weekday (circle one): M T W Th (F) Sat Sun

Recorded By (circle one): (Mother) Father Other_____

Local Code:_____
(Office use only)

TEDDY
3-Day Diet

EXAMPLE 2

What time/ where did your child eat?	What did your child, eat/ drink? • Use 1 line per food/drink • Include vitamins and water	How much did your child eat/drink? • Include units (oz., tbs., tsp., cups, etc.)	Brand Name/ Preparation • Was anything added? • How was the food/drink prepared? • If the food was prepared, what were the ingredients? • Milk: indicate if breast milk, formula, cow's milk, etc.
(am) 7:00 pm (Home) Other	Yogurt	4 oz.	Yoplait Custard Style-Strawberry
	MultiGrain Cheerios	1/4 cup	Dry cereal, no milk added
	Milk	6 fluid oz	Horizon Whole milk Plus DHA from sippy cup
(am) 10:00 pm (Home) Other	Goldfish	8 pieces	Pepperidge Farm Goldfish-Original Brand
	Pear	1/4 of pear	Cut up into small chunks: 12 chunks (2x2x4)
	Water	5 fluid oz	Tap water from sippy cup
am 12:00 (pm) Home (Other)	Turkey	1 slice	Boar's Head Low Sodium Turkey Breast; Thin slices cut in pieces
	Green beans	6-8 beans	Del Monte No salt Added cut green beans
	Cheese	1 slice	Kraft 2% Single Slices- American
	Milk	6 fluid oz	Mayfield Whole Milk from sippy cup ↪ **continue on the back**

EXAMPLE 2 (continued)

What time/ where did your child eat?	What did your child, eat/ drink?	How much did your child eat/drink?	Brand Name/ Preparation
am 3:00 (pm) (Home) Other	Nutra Grain Bar	1 bar	Kellog's Nutri Grain Cereal Bar-Blueberry
	Water	6 fluid oz	From Tap
	Mandarin Oranges	1 snack cup	Del Monte 4oz snack size in light syrup
am 6:00 (pm) (Home) Other	Chicken Breast	1/2 cup	Purchased rotisserie chicken breast cut up into small pieces
	Macaroni and Cheese	1/2 cup	Kraft Macaroni and Chhese made with 2% milk and Shedd's Spread Country Crock Omega Plus Light
	Broccoli	2 florets	Steamed with no seasoning or butter
	Milk	6 fluid oz	Mayfield Whole Milk from Sippy cup
am _____ pm (Home) Other			
am _____ pm (Home) Other			

Date: 10-29-2004

Weekday (circle one): M T W Th (F) Sat Sun

Recorded By (circle one): (Mother) Father Other_____

Local Code: _____
(Office use only)

TEDDY
3-Day Diet

EXAMPLE 3

What time/ where did your child eat?	What did your child, eat/ drink? • Use 1 line per food/drink • Include vitamins and water	How much did your child eat/drink? • Include units (oz., tbs., tsp., cups, etc.)	Brand Name/ Preparation • Was anything added? • How was the food/drink prepared? • If the food was prepared, what were the ingredients? • Milk: indicate if breast milk, formula, cow's milk, etc.
(am) pm 7:00 (Home) Other	Cereal	1/2 cup	Berry Berry Kix
	Milk	1/4 cup	2% Milk added to cereal
	Banana	1/2 banana	Small banana (6 inch) added to cereal
	Multivitamin	1 tablet	Flintstone's Complete Multivitamin Plus Iron
(am) pm 10:30 (Home) Other	Graham crackers	2 squares	Keebler Honey Grahams 2 x 2 squares
	Peanut butter	2 tbls	Jiffy peanut butter added to crackers
	Apple Juice	6 fluid oz	Juicy Juice from cup
am (pm) 12:30 Home (Other)	Grilled Cheese	1/2 sandwich	Kraft American Cheese Deluxe 2% with whole wheat bread
	Green beans	6-8 beans	Del Monte No salt Added cut green beans
	Chips	6 chips	Baked Lays barbeque potato chips
	Milk	6 fluid oz	2% Milk from cup
			↪ continue on the back

EXAMPLE 3 (continued)

What time/ where did your child eat?	What did your child, eat/ drink?	How much did your child eat/drink?	Brand Name/ Preparation
am (pm) 3:00 (Home) Other	Carrot sticks	4 sticks (4x4x4)	Raw baby carrot sticks with 4 tsp Hidden Valley Fat-Free Ranch dressing
	Water	6 fluid oz	From Tap
am (pm) 6:00 Home (Other)	McDonalds Chicken Nuggets	4 pieces	Chicken Nuggets with 1 package of honey mustard sauce
	French fries	1 small order	McDonald's fries, 1 small order
	Milk shake	Childs size	McDonald's Chocolate shake; only finished .5 of it
	Water	6.5 oz	AquaFina bottled water
am _____ pm Home Other			
am _____ pm Home Other			

Date:_____

Weekday (circle one): M T W Th F Sat Sun

Recorded By (circle one): Mother Father Other_____

TEDDY
3-Day Diet

Day 1

What time/ where did your child eat?	What did your child, eat/ drink? * Use 1 line per food/drink * Include vitamins and water	How much did your child eat/drink? * Include units (oz., tbs., tsp., cups, etc.)	Brand Name and Manufacturer/ Preparation * Was anything added? * How was the food/drink prepared? * If the food was prepared, what were the ingredients? * Milk: Indicate if breast milk, formula, cow milk (1%, 2%, whole), soy milk (fortified), etc * Fat used in preparation.: Indicate butter or margarine: stick, spread or spray; % of fat, and any additions such as calcium or omega 3.
am _____ pm Home Other			
am _____ pm Home Other			
am _____ pm Home Other			

B. Day Care Food Intake Form

Finland (in Finnish)

TEDDY -tutkimus

6 KK IKÄISEN LAPSEN RAVITSEMUS
Ruokapäiväkirja lapsen hoitopaikkaa varten

Tutkimushoitaja täyttää

Lapsen koodi _____

Lapsen nimi _____

Lapsen syntymäaika ____/____/____

HYVÄ HOITOHENKILÖKUNTA!

Hoitolapsenne osallistuu TEDDY-tutkimukseen. Lapsen vanhemmat kirjaavat lapsen kotona syömät ruoat. Pyydämme teitä ystävällisesti kirjaamaan huolellisesti **kaikki hoitolapsenne päivähoidossa syömät ruoat ja juomat ruokapäiväkirjaan seuraavien päivien aikana:**

_____ _____ _____; _____ _____ _____; _____ _____ _____.

Jotta lapsen syömien ruokien valmistusaineista ja –tavoista saataisiin mahdollisimman tarkat tiedot, **toivomme ruoan valmistuksesta vastaavien henkilöiden yhteistyötä lapsen ruokien kirjaamisessa.**

Pyydämme teitä tutustumaan oheisiin kirjanpito-ohjeisiin ennen ensimmäistä kirjanpitopäivää. Älkää antako ruokapäiväkirjan pidon vaikuttaa lapsen ruokavalioon. Palauttakaa ruokapäiväkirja molempien kirjanpitopäivien jälkeen lapsen vanhemmille. Hoitolapsenne mukanaolo tutkimuksessa on ensiarvoisen tärkeää, joten yhteistyönne on hyvin arvokasta.

Jos teillä on kysyttävää tutkimuksesta tai ruokapäiväkirjan täyttämisestä, ottakaa yhteyttä hoitolapsen vanhempiin.

KIITOS AVUSTANNE!

Lapsen hoitopaikka on:

1. Päiväkoti
2. Perhepäivähoitaja
3. Hoitaja lapsen kotona
4. Lapsen isovanhempi
5. Muu, mikä _____

Päiväkodin nimi _____ Puh.____/_____

Valmistetaanko päiväkodissa tarjottava ruoka jossain muualla?

1. Kyllä, ruoka valmistetaan_____
   Puh.____/_____
2. Ei, ruoka valmistetaan hoitopaikassa

Vastaavan keittäjän nimi_____Puh._____/_____

Ruokapäiväkirjan täyttäjä/täyttäjät:

_____Puh.____/_____

_____Puh.____/_____

PÄIVÄMÄÄRÄ |1|4|0|9|2016| VIIKONPÄIVÄ: Torstai Lapsen nimi: Matti
p p k k v v

Aika ja paikka	Ruoat ja juomat	Kauppanimi tai valmistusaineet Valmistustapa	Syöty/juotu määrä
8.00 hoitopaikka	Kaurapuuro	kaurahiutaleet ja vesi, keitetty, ei suolaa	½ dl
	Ruusunmarja-vadelmasose	Nestlé Piltti (>4 kk)	2 tl
11.00 hoitopaikka	Naudanliha-kasvissose	naudanjauheliha (1/4), peruna (1/2) ja porkkana (1/4) keitetty vedessä, soseutettu, nesteenä keitinvesi, ei lisätty suolaa	½ dl
	Äidinmaidonkorvike	Nutricia Tutteli Plus 1 (0-6kk), nestemäinen	½ dl
12.30 hoitopaikka	Äidinmaidonkorvike	Nutricia Tutteli Plus 1 (0-6kk), nestemäinen	¾ dl
15.00 hoitopaikka	Peruna-parsakaalisose	peruna (1/2) ja parsakaali (1/2) keitetty vedessä, soseutettu, nesteenä keitinvesi, ei lisätty suolaa	½ dl
	Rypsiöljy	Kultasula	1 tl
	Hedelmiä ja jogurttia	Nestlé Bona (> 5-6 kk)	2 rkl

Muista merkitä nämä:

Nestemäinen ruoka:

-äidinmaito

-äidinmaidonkorvike ja sen kauppanimi

-muu maito ja sen laatu

-vesi, mehu, muu juoma

Kiinteä ruoka:

- hoitopaikassa tai kotona valmistettu: valmistusaineet ja -tapa

- valmisruoka: kauppanimi, valmistaja

-muu ruoka, esim. maistiaiset

Lisäravintovalmisteet, lääkkeet

PÄIVÄMÄÄRÄ |_|_|_|_|20|_|_| VIIKONPÄIVÄ _____ Lapsen nimi:_____
p p k k v v

Aika ja paikka	Ruoat ja juomat	Kauppanimi tai valmistusaineet Valmistustapa	Syöty/juotu määrä

Muista merkitä nämä:

Nestemäinen ruoka:

-äidinmaito

-äidinmaidonkorvike ja sen kauppanimi

-muu maito ja sen laatu

-vesi, mehu, muu juoma

Kiinteä ruoka:

- hoitopaikassa tai kotona valmistettu: valmistusaineet ja -tapa

- valmisruoka: kauppanimi, valmistaja

-muu ruoka, esim. maistiaiset

Lisäravintovalmisteet, lääkkeet

Germany (in German and English)

Art der Kinderbetreuung:

- ☐ Kindertagesstätte / Hort / Kindergarten
- ☐ Tagesmutter
- ☐ Babysitter / Großeltern
- ☐ Andere, bitte beschreiben Sie ___________________________

Name der Einrichtung: _________________________________

Tel.: _______/____________

Wurden die Mahlzeiten, welche an den zu protokollierenden Tagen verzehrt wurden, woanders zubereitet?
Mehrere Antworten möglich:

- ☐ Ja, Speisen / Getränke werden dem Kind von zu Hause mitgegeben
- ☐ Ja, Speisen werden komplett zubereitet und warm geliefert von

  Name: ________________________
  Kontaktperson: ________________________
  Tel.: ________/___________

- ☐ Ja, Speisen werden zubereitet von

  Name: ________________________
  Kontaktperson: ________________________
  Tel.: ________/___________

  und in der Betreuungseinrichtung erwärmt.

- ☐ Ja, Speisen werden von oben genanntem Unternehmen zubereitet und mit eigenen Speisen oder Getränken ergänzt (weiter siehe unten)

- ☐ Nein, die Speisen werden in der Betreuungseinrichtung zubereitet

  Name:________________________________
  Tel.: ________/_______________

Das Protokoll wurde geführt von:

__________________________________ Tel.:_______/________________

Ernährungsprotokoll von [Name]

Datum: ________________

Bitte geben Sie die Namen der verzehrten Lebensmittel, Getränke und der ggf. eingenommenen Medikamente möglichst genau an. Denken Sie bitte auch an Wasser zum Trinken und zur Zubereitung von Speisen. Wir benötigen auch Angaben zum Fettgehalt (Milch, Käse, Wurst) oder zum Fruchtgehalt (Saft, Nektar) sowie Zusätze von Vitaminen.
Sammeln Sie bitte die Verpackungen der Produkte und überreichen diese mit dem Protokoll den Eltern!

Wann? Uhrzeit	Wo? Ort	Was? Gefäß/+Lebensmittel bzw. Getränk; Nährstoffpräparate, Medikamente	Wie viel? g	Rest g

Type of day care:

- ☐ Day-care center / nursery / kindergarten
- ☐ Day mother
- ☐ Babysitter / grandparents
- ☐ other, please describe ______________________

Childcare facility's name: ____________________________

Phone: ______/___________

Were the foods consumed during record keeping prepared somewhere else?
More than one answer possible:

- ☐ Yes, meals / beverages were taken from child's home
- ☐ Yes, meals have been prepared and supplied warm completely by

  Name: ____________________
  Contact person: ____________________
  Phone: _______/__________

- ☐ Yes, meals were prepared by

  Name: ____________________
  Contact person: ____________________
  Phone: _______/__________

  and heated up at childcare facility.

- ☐ Yes, meals are prepared by above-named caterer and completed by meals or beverages prepared at day care (continue below)

- ☐ No, meals are prepared at day care facility

  Name: ___________________________
  Tel.: _______/_____________

The record was kept by:

_____________________________ Phone: ______/_____________

Dietary record from: _______________

Date: ___________

Please write down all foods, beverages, medications or dietary supplements and describe them as accurately as possible. Remember drinking water or water for food preparation. We need information e.g. about the fat content (milk, cheese, cold meat) or about the fruit content (juice, nectar) as well as fortified vitamins.

Please keep the packages of the foods and hand them over with the record!

When? Time	**Where?** Place*	**What?** container/+ food or beverages; vitamin/mineral preparations, medications	**How much prepared?** g	**Left over** g

Sweden (in Swedish and English)

MATDAGBOK - BARNOMSORG

Barnets namn ..... Local code .....

Vilken veckodag registreras barnets mat (ringa in)?

mån tis ons tors fre Datum .....

Om det behövs så använd flera blad. Börja varje ny dag på ny sida!

Detta är sidan .... av .... sidor.

När åt eller drack barnet?	Beskriv vad barnet åt och drack. Ange fabrikat, tillagningssätt, typ av fett, salt etc (om det behövs, så använd flera rader)	Kökenkans kommentar	Hur mycket fick barnet?	Hur mycket åt barnet?

FOOD RECORD FORM – DAY CARE

The Childs name ..... Local code .....

What day of the week is covered in the food record (circle one)?

Mon Tue Wed Thu Fri Date .....

If needed, use more pages. Start each day on a new page!

This is page .... of .... pages.

What time did the child eat or drink?	Describe what the child ate or drank. Report cooking method (fried, boiled), fat used when frying, brand names, and if salt is used.	Notes from the kitchen	How much did the child get (at the plate)?	How much did the child eat?

US

Date:_____ Child's Name: _____ Day Care Diet Page 1

Weekday (circle one): M T W Th F Sat Sun

Recorded By (Name): _____

Day

What time/ where did the child eat?	What did your child, eat/ drink? ★ Use 1 line per food/drink ★ Include vitamins and water	How much did your child eat/drink? ★ Include units (oz., tbs., tsp., cups, etc...)	Brand Name/ Preparation ★ Was anything added? ★ How was the food/drink prepared? ★ If the food was prepared, what were the ingredients? ★ Milk: indicate if breast milk, formula, cow's milk, soy milk, flavor, etc. ★ Fat: indicate butter or margarine, include stick or spread, % of fat, any additions to the product such as omega-3 or calcium.
am _____ pm Day 1			
am _____ pm Day 2			

Date:_____ Child's Name: _____ Day Care Diet Page 2

Weekday (circle one): M T W Th F Sat Sun

Recorded By (Name): _____

Day

What time/ where did the child eat?	What did your child, eat/ drink? ★ Use 1 line per food/drink ★ Include vitamins and water	How much did your child eat/drink? ★ Include units (oz., tbs., tsp., cups, etc...)	Brand Name/ Preparation ★ Was anything added? ★ How was the food/drink prepared? ★ If the food was prepared, what were the ingredients? ★ Milk: indicate if breast milk, formula, cow's milk, soy milk, flavor, etc. ★ Fat: indicate butter or margarine, include stick or spread, % of fat, any additions to the product such as omega-3 or calcium.
am _____ pm Day 3			

C. 24-hour Recall and Food Interviewer Assessment Form

Dietary Interviewer: _____ Site: _____

Date of Observation: _____

Baseline or Final (circle)In-person or Telephone recall (circle)

Set-up and Process	Satisfactory (S) Needs Improvement (NI) Not Applicable (NA)
1. Computer set-up and ready-to-go	
2. Forms and materials available	
3. Introduces himself/herself, establishes rapport	
4. Explains task	
5. Shows or references participant to amount estimation tools	
6. Demonstrates knowledge of foods and local food supply	
7. Demonstrates knowledge of dietary supplements	
8. Demonstrates ability to answer participants' questions about foods and nutrients	
9. Demonstrates ability to use the computer software without compromising interview time and positive environment	
9. Thanks the participant	
Comments or Concerns on Set-up and Introduction	

Interviewing Technique and Overall Assessment	Satisfactory (S) Needs Improvement (NI) Not Applicable (NA)
1. Motivates the participant and leads the interview	
2. Uses open-ended questions	
3. Maintains a comfortable pace	
4. Remains neutral throughout the interview	
5. Uses notes to document questionable foods and amounts	
6. Understands the database and can find foods quickly	
General Comments or Concerns of Overall Assessment and Interviewing	

D. Description of the Nutrient Databases

USA: NDS-R

University of Minnesota, Nutrition Coordinating Center, Division of Epidemiology Nutrition Data System (NDS)

Page URL: *http://www.ncc.umn.edu/*

Telephone: 612-626-9450
Fax: 612-626-9444
NDS Software E-mail: ncc@epi.umn.edu
NCC Service Center E-mail: nccservicecenter@epi.umn.edu

The first version to be used in TEDDY will be NDS-R version 5.0_35 (2004)

The NDS software features built-in, standard prompts for obtaining detailed food descriptions, including preparation method and ingredient information. The NDS-R requires specialized training and extensive practice in order to effectively utilize it to conduct a research interview. The NDS-R software calculates the nutrients reported by each participant and provide daily total counts of the number of servings of fruit, vegetables and beverages consumed for each diet day. A standardized multiple-pass approach is used by all TEDDY dietary interviewers to collect the 24-hour dietary recalls and the 3-day food records.

Values for up to 130 nutrients, nutrient ratios and other food components are available. The most comprehensive research version of NDS converts amounts of foods reported to gram weights and calculates nutrients, which include energy, protein, fat, carbohydrate, alcohol, water, ash, animal and vegetable protein, 18 amino acids, 23 individual fatty acids, cholesterol, starch, six simple sugars, total dietary fiber and three fiber fractions, nine minerals, vitamins, caffeine, saccharin, aspartame, oxalic acid, trans fatty acids, carotenoids, and phytates. Dietary supplements and medications containing caffeine and sodium are included. NDS calculates nutrient intake and presents the data in several formats, including daily nutrient totals; nutrient amounts per individual food; and daily totals compared to the RDAs.

The Nutrition Coordinating Center at the University of Minnesota maintains extensive documentation about the NDS-R data fields, their derivations, and the laboratory assays on which they are based, as well as training and certification standards for NDS-R users. For additional information, refer to the NDS-R software documentation.

Germany: LEBTAB Nutrient Database

The Diabetes Research Institute in Munich uses the food database known as LEBTAB, which was developed and is in use at the Research Institute of Child Nutrition (FKE) in Dortmund, Germany for the DONALD Study (Dortmund Nutritional and Anthropometric Longitudinally Designed Study) (*http://www.fke-do.de/method1.html*)

Address and contact person:

PD Dr. Mathilde Kersting
Research Institute of Child Nutrition
Heinstück 11, 44225 Dortmund, Germany
Phone: +49-231-7922 10 18

Nutrients that can be evaluated by the database energy, water, protein, protein-animal, fat, saturated fatty acids, linoleic acid, polyunsaturated fatty acids, monounsaturated fatty acids (by difference), cholesterol, carbohydrates, fibre total, sugars added, calcium, magnesium, phosphorus, iron, zinc, copper, manganese, retinol, carotenoids, tocopherols, vitamin B1, vitamin B2, vitamin B6, niacin, folate, ascorbic acid, vitamin D.

For some foods (e.g. noodles, rice) but not for vegetables etc. data on cooked food are available. For other food items standard factors are used, by which raw food can be converted into cooked food. For each food item an average loss in nutrients by cooking, preparing and storage of food is calculated (there are standards for each nutrient developed by the German society for nutrition, 1).

There are several possibilities of food groupings: milk, meat, fish, eggs, bread and cereals, cow's milk can be divided into fresh milk, milk powder (contained in commercial products), yoghurts, cheese etc. This is done by coding food-items before data entry. With the software of the FKE we are able to assess for example the total milk consumption including the amounts of milk used as ingredients in recipes or the content of powdered milk in many food products.

Finland: Fineli/Finessi

The TEDDY nutritionists at National Public Health Institute in Helsinki use the Finessi program to enter the data into Fineli food database. The Fineli database is developed and owned by the National Public Health Institute in Helsinki, Finland.

Address and contact person:

M.Sc. Carina Kronberg-Kippilä

National Public Health Institute

Mannerheimintie 166, 00300 Helsinki, Finland

Phone: +358 9 4744 8734

The calculated nutrients are: energy (kJ), water, alcohol, nitrogen, protein, carbohydrates (available), carbohydrates (difference), fiber, insoluble fiber, soluble fiber, starch, sugars, total fats, fatty acids (all), cholesterol, saturated fatty acids, monounsaturated (cis) fatty acids, unsaturated fatty acids, linolenic acid, n – 3 fatty acids, n – 6 fatty acids, fatty acid 22:6 n – 3 (DHA), fatty acid 20:5 n – 3 (EPA), vitamin A (RE), beta-carotene equivalent, carotenoids, vitamin E (TE), gamma-tocopherol, vitamin C, vitamin D, 25-hydroxy-calsiferol, ergo/cholecalsiferol, thiamine (B_1), riboflavin (B_2), pyridoxine, niacin (nicotine acid + nicotine amide), niacin equivalent, vitamin (B_{12}) folate (HPLC), folate (microbiologic assay), panthotenic acid (B_5), biotin, vitamin K, potassium, calcium, phosphorus, magnesium, iron, zinc, selenium, manganese, nitrate, nitrite, sodium, copper and iodine.

The losses of nutrients and the losses at food preparation are taken into account in the calculations. The losses at food preparation are taken into account when recipes are entered or modified.

The food items can be grouped either by food use classes or by ingredient classes.

Food use classes:

- FRUDITOT Fruit and berry dishes (total)
  - FRUFRESH Fresh fruit
  - FRUBSAL Fruit and berry salads
  - BERFRESH Fresh berries
  - FRUBSOUP Fruit and berry soups
  - FRUBPAST Fruit and berry pastries
  - FRUBJUIC Fruit and berry juices
  - JAM
- VEGDITOT Vegetable dishes (total)
  - VEGFRESH Fresh vegetables (raw)
  - VEGPOT Prepared vegetables (e.g. boiled)
  - VEGDISH Vegetable dishes (main)
  - VEGCASS Vegetable casseroles
  - VEGSOUP Vegetable soups

    - MUSHRDI Mushroom dishes
    - VEGCANN Canned vegetables
    - VEGJUICE Vegetable juices
- SALADTOT Salads (total)
    - SALADVEG Vegetable salads
    - SALADMIX Mixed salads
- POTATOT Potato
    - POTACOOK Cooked potatoes
    - POTADISH Potato dishes
    - POTAFAT Fried potatoes, cream potatoes
- CEBAKTOT Cereal and bakery products (total)
    - BRMIX Mixed bread, bread with seeds
    - BRWHITE White bread
    - BRRYE Rye bread
    - BUN
    - BAKSWEET Sweet pastries
    - BISCUIT
    - BAKSALT Salty pastries
    - SANDWICH (incl. hamburgers)
    - RICEADD Rice (as side dish)
    - PASTAADD Pasta dishes
    - PORR Porridge
    - CERBRKF Breakfast cereals
    - CERPR Pastries etc. miscellaneous
    - PIZZA
- MILKDTOT Milk dishes (total)
    - MILKFF Milk, fat free
    - MILKLF Milk, fat <2%
    - MILKHF Milk, fat >2%
    - SMILK Sour milk
    - YOGHURT
    - MILKCURL Cultured milk
    - CHEESHAR Hard cheeses
    - CHEESOFT Soft cheeses
    - VEGCHEES Cheeses with vegetable fat
    - ICECREAM
    - MILKPUDD Milk puddings
    - MILKSAUC Milk sauces
- FATTOT Fat (total)
    - BRFBUTT Butter, milk fat products, fat >60%
    - BRFMARG Bread fat, margarine, fat >55%
    - BRFLOWF Low fat bread fat, margarine, fat <55%
    - DRESSING
    - FATPROD Other fat products
    - FATSAUCE Fat sauces
- EGGDISH
    - EGGS

    - EGGMIX Egg dishes
- FISHDTOT Fish dishes (total)
    - FISH
    - FISHCASS Fish casseroles
    - FISHSOUP Fish soups
    - FISHDOTH Other fish dishes
    - FISHPROD Fish products
- MEATDTOT Meat dishes (total)
    - MSTEAK Meat, steaks
    - MINCMED Minced meat dishes
    - MEATPOT Meat stews
    - MEATCASS Meat casseroles
    - MEATSOUP Meat soups
    - POULTDI Poultry dishes
    - SAUSAGE
    - SAUSDISH Sausage dishes
    - OFFALDI Offal dishes
- BEVTOT Beverages (total)
    - COFFEE
    - TEA
    - DRWATER Drinking water
    - DRJUICE Juices
    - DRINKSO Soft drinks
    - DRINKCO Soft drinks with caffeine
    - DRINKART Artificially sweetened drinks
    - DRSPORT Sport drinks
- ALCTOT Alcohol drinks (total)
    - BEER
    - WINE
    - SPIRIT
    - ALCOTH Other alcohol drinks
- SUGARTOT Sugar and sweets (total)
    - SUGADD Sugar, syrups
    - SWEET
    - CHOCOL Chocolate
- MISCTOT Miscellaneous (total)
    - SPICES
    - SNACK
    - SPISAUCE Spiced sauces
    - INGRMISC Miscellaneous ingredients
- BABYFTOT Baby foods (total)
    - BABMEATD Meat dish for babies
    - BABFISHD Fish dish for babies
    - BABMILPO Milk porridges for babies
    - BABWATPO Water porridges for babies
    - BABFRUB Baby fruit and berry dish
    - BABVEGE Baby vegetable dish

- BABMIFRU Baby fruit and milk
- BABOTHER Other baby foods

- SPECTOT Supplements (total)
  - SPECFOOD Clinical supplements
- MMILK Formulas
  - INFMILK Infant milk formulas (regular)
  - CASMILK Infant milk formulas (casein hydrolyzed)
  - PREMILK Formulas for premature
  - SOYMILK Soy formulas
  - WHEYMILK Infant milk formulas (whey has been hydrolyzed)
  - AMINMILK Infant milk formulas (protein hydrolyzed to amino acids)

Ingredient classes:

* ALCTOT Alcohol drinks
  - o ALCOTH Other alcohol drinks
  - o BEER
  - o SPIRIT
  - o WINE
* BEVTOT Beverages (total)
  - o COFFEE
  - o SDRINK Soft drinks
  - o TEA Tea
  - o WATER
* CERTOT Cereals (total)
  - o BISCUIT
  - o BRHARD Hard bread
  - o CEROTH Other cereals
  - o OATBAR Oat, barley
  - o PASTA Pasta, macaroni
  - o RICE
  - o RYE
  - o STARCH
  - o WHEAT
* DIETTOT Dietary supplements (total)
  - o ANTROPOS Antroposofic supplements
  - o BABYFOOD
  - o ENZYMES Enzyme supplements

- o FATSUPPL Fat supplements (incl. lecithin)
- o FIBSUPPL Fiber supplements
- o HERBSUP Herbal supplements
- o HOMEOS Homeopathic supplements
- o MINSUPPL Mineral supplements
- o MMILK Formulas
- o PROBPREB Probiotic and bacteria supplements
- o SPECFOOD Clinical supplements
- o VITMISUP Vitamin and mineral supplements
- o VITSUPPL Vitamin supplements
- o YEAST Yeast preparations

* EGGTOT Egg (total)
  - o EGG
  - o EGGOTH Eggs of other bird species
* FATTOT Total fat
  - o BUTTMIX butter, mixtures of milk fat
  - o FATANIM Animal fat
  - o FATHARD Fats for food preparation and industry
  - o FATLVEG Margarine, fat <55%
  - o FATOTH Other fats
  - o FATVEG Margarine, fat >55%
  - o OIL
* FISHTOT Fish (total)
  - o FISH Kalat
  - o FISHPROD Fish products
  - o SHELLFIS Shellfish
* FLAVTOT Spices
  - o FLAVSAUC Flavored sauces
  - o FLAVSEED Flavored seeds
  - o HERB Dried herbs
* FRUITTOT Fruit (total)
  - o BERRY
  - o CITRUS

- o FBDRINK Fruit based drinks
- o FRUITCAN Canned fruit
- o FRUITOTH Other fruit
- o JUICE
- o APPLE Apple fruit

* INDTOT Industrial food (total)
  - o INDMEAL Industrial meals
  - o SNACK
* INGRTOT Ingredients (total)
  - o INGRMIS Miscellaneous ingredients
  - o SALT
  - o SWEAGE Sweeteners
* LEGUTOT Legumes (total)
  - o NUTSEED Nuts, seeds
  - o PEABEAN Peas, beans
  - o SOYAPROD Soya products
* MEATTOT Meat (total)
  - o BEEF
  - o GAME
  - o LAMM
  - o MEATPROD Meat products
  - o OFFAL
  - o PORK
  - o POULTRY
  - o SAUSAGE
* MILKTOT Milk total
  - o CHEESE
  - o CREAM
  - o ICECREAM
  - o MILK
  - o MILKOTH Other milk
  - o SMILK Sourmilk
* NONINGR Non ingredients

- o DISH

* POTATOT Potato (total)
  - o POTAPROD Potato products
  - o POTATO
* SUGARTOT Sugar and sweets (total)
  - o CHOCOLAT
  - o SUGAROTH Other sugars
  - o SUGARSYR Sugars and syrups
  - o SWEET
* VEGTOT Vegetables (total)
  - o CABBAGE
  - o MUSHRO Mushrooms
  - o ROOT
  - o VEGCANN Canned vegetables
  - o VEGFRU Vegetable fruit
  - o VEGLEAF Leafy vegetables
  - o VEGONI Onion vegetables

Sweden: National Food Database

The food database for Sweden is the National Food Database, owned by the National Food Administration (www.slv.se). This national database contains national values for some 1800 foods and food dishes. For every food in the database values for over 50 nutrients are listed. Values are also given for other vitamins, trace elements and bioactive compounds in 250-300 foods. It shows the content of nutrients in edible part of the food.

For every food in the database values for over 50 nutrients are listed. Values are also given for other vitamins, trace elements and bioactive compounds in 250-300 foods. Gram, milligram and microgram are the units used. Nutrients included are: energy (kcal and kJ); waste products; ash; alcohol; at (saturated fat, mono- and polyunsaturated fatty acids, cholesterol), carbohydrates (mono- and disaccarides, sucrose, fiber); protein; fat soluble vitamins (Vitamin D, carotene; retinal equivalents, α-tocopherol); water soluble vitamins (Ascorbic acid, folate, niacin, niacin equivalents, riboflavin, thiamin; vitamin B6, Vitamin B12); minerals (P, Fe, Ca, Na, K, Mg, Se, Zn).

The calculation and database front end program for TEDDY dietary data from Sweden is a commercial software program. The calculations are done by a dietitian.

E. Comparison of Nutrient Databases

At the inception of the TEDDY project, the Diet Committee made extensive comparisons of data fields and calculation parameters for the various nutrients and databases. These comparisons for nutrients and food groups have been incorporated into two MS Excel worksheets which are output to Adobe .pdf files and incorporated as addenda to Chapter 13 of the TEDDY MOO.

For the most part, nutrients are comparable and consistently calculated by the various databases in use for TEDDY. The most critical nutrients in terms of compatibility are fiber and folate, as the literature suggests that values analyzed by different methods can not be converted to be mutually comparable. If fiber and/or folate become nutrients showing significance in the outcomes analysis, then further calculations will be necessary in an effort to remove any systematic bias that may arise from different laboratory methods used to calculate methods.

Another item to note is that the German database LEBTAB does not include information for the mineral selenium. This is not considered to be a major deficiency. For the TEDDY project, selenium is measured from toenail clippings, beginning when the child is age 2 years and then collected every 2 years after that. This is a reliable biomarker for tissue selenium. Dietary selenium is obtained from consuming fruits, grains, nuts and vegetables that are grown in selenium-rich soil. As selenium lies beneath sulfur on the periodic table of the elements, it follows that any plant that absorbs sulfur from the soil also has an affinity to absorb selenium if it is present in the soil. But the selenium content of soils across the globe is highly variable, and dietary selenium is very difficult to measure even under the best circumstances; to get an accurate measure, one must know the selenium content of the soil where a particular plant has grown. For example, onions are a high-sulfur vegetable that will accumulate selenium. But onions grown in California (high selenium soils) will have a different content of the mineral than onions grown in Florida or Michigan (low selenium soils).

The different databases and software programs also place various foods into different food groups. For example, databases for Germany, Sweden and Finland have a separate food group called *potatoes* or *potato products*. The USA database NDS groups potatoes together with rice and pasta in a combined group. In another example, NDS has a food group called *Fats, oils, and nuts.* Germany groups these foods as *Fats and fatty sauces*; Sweden groups these foods as *Fats & Oils*; and Finland groups them as *Fat and fat products.* These differences in food groups, some of which are seemingly small, need to be reconciled during outcomes analysis in order to ensure consistent representation and accuracy in charactering food intakes in the four different countries.

The output of MS Excel spreadsheets with nutrient and food group information or the four databases are contained in separate Adobe Acrobat .pdf files that are addenda to this chapter.

13. Clinical Measurements

All staff working with TEDDY participants must recognize and support the needs not only of the TEDDY child but also the parents/primary caretaker and siblings

Environment:
For families to participate in TEDDY clinic visits, it may be necessary for parents/primary caretakers to bring other children to the clinic. The environment should be conducive to promoting safety with adequate space to accommodate additional family members especially children. Quiet activities should be available to help entertain the TEDDY child and any other children. The space and activity items should be easy to clean and safe for all ages.

All space should promote confidential interactions and have separate areas to prevent children overhearing any other children undergoing testing which may be difficult and upsetting to hear.

Clinic visits should be completed in a timely manner as children become bored quickly, and to prevent disruption of naps, meals and snacks.

Procedures such as height and weight can be made into a game and fun for the children.

It is hypothesized that initiation of persistent islet autoimmunity and progression from islet autoimmunity to diabetes is increased with excessive weight gain or accelerated growth. In order to test this hypothesis, weight and height will be assessed at each clinic visit as listed in Table 9.2 (Section 9) Visit Schedule and Summary of Contents.

13.1. Length (Children below the age of 2 years old)

1. Length will be measured with an Infantometer.
   - It is NOT a requirement for all TEDDY clinical sites to use the same equipment.
   - Preferably the same brand and model would be used within a site.
2. The measuring device should be covered with a clean paper shield before placing the infant on it.
3. The child shall be laid on the measuring instrument with the head abutted to the stationary platform by an assistant. The top of the external auditory meatus (ear canal) should be on the same level with the inferior margin of the bony orbit (cheekbone), that is the head should not be tilted in any direction. The shoulders, pelvis and legs will be held in contact with the infantometer and the moving platform will be used to ensure that the feet are square to the instrument. The heels and balls of the feet and the toes should all be touching the moving platform.
4. If a subject cannot be positioned in the standard manner, (e.g. clubfoot) a note should be made to describe how the positioning during measured differed from standard, so that the same modification be used at subsequent visits. If a child has asymmetrical leg lengths, the length will be measured to the heel of the longer leg.

5. Length is measured from the heels to the top of the head avoiding toe pointing. It is preferable that one person is checking the position of the lower extremities while a second person ensures the head remains secure.
6. Read measurement to the nearest 0.1 cm and document the length in centimeters (cm) on the Physical Examination Form.

   NOTE: Only lengths measured specifically for TEDDY should be indicated on the Physical Exam Form; lengths measured at regular health care provider visits should be indicated on the TEDDY Book extraction form.

   If subject is a Long-Distance Protocol subject site should mark the radio button "Weight & Length/Height collected by long-distance protocol", mark either "by healthcare professional" or "by parent" and enter the date of measurement.

   If subject is not on the Long-Distance Protocol, but the length measurement occurred outside of the TEDDY clinic, site should mark the radio button "Weight & Length/Height collected by non-standard TEDDY protocol", mark either "by healthcare professional" or "by parent" and enter the date of measurement.

7. After measurement is complete, clean Infantometer per manufacturer's recommendations.

13.2. Height (Children able to stand on their own for measurement)

1. Height will be measured with a wall mounted Stadiometer or other standardized device for measuring height.
   - It is NOT a requirement for all TEDDY clinical sites to use the same equipment.
   - Preferably the same brand and model would be used within a site.
2. Child must remove shoes before height measurement, but may wear socks. Hair barrettes, ribbons, hats, etc. should be removed if they or the tuft of hair they create come in contact with the stadiometer, or otherwise interfere with head position. Thick haircuts should be flattened as much as possible before recording height.
3. Child should look straight ahead while standing with the back against the Stadiometer. The knees should be straight, feet together, heels on floor and with head, shoulder blades, buttocks, and heels touching the wall.
4. Grasp headboard firmly near knob and loosen knob. The top of the external auditory meatus (ear canal) should be at the same level as the inferior margin of the bony orbit (cheekbone), that is the head should not be tilted either front to back or to the side. Hold the head in place by gently placing one hand along both sides of the lower jaw. Be careful not to apply traction.
5. Lower headboard to rest against crown of the head and tighten knob.

6. Read measurement to the nearest 0.1 cm as noted by the thin black line of the headboard on the measuring backboard. Measurement readings are most accurate when the examiner's eye is in line with the line on headboard, which is not looking up to or down on the line.
7. Document height in centimeters (cm) on the Physical Examination Form.

   NOTE: Only heights measured specifically for TEDDY should be indicated on the Physical Exam Form; heights measured at regular health care provider visits should be indicated on the TEDDY Book extraction form. Heights entered on the Physical Exam Form can be completed +/- 30 days from the date of the TEDDY visit to allow for Long-Distance Protocol measurements, satellite site measurements, etc.

   If subject is a Long-Distance Protocol subject site should mark the radio button "Weight & Length/Height collected by long-distance protocol", mark either "by healthcare professional" or "by parent" and enter the date of measurement.

   If subject is not on the Long-Distance Protocol, but the height measurement occurred outside of the TEDDY clinic, site should mark the radio button "Weight & Length/Height collected by non-standard TEDDY protocol", mark either "by healthcare professional" or "by parent" and enter the date of measurement.

8. Center practices varied in calibration frequency and method.

13.3. Weight

Scales used to measure weight, whether digital or beam, are to be calibrated for accuracy on a monthly or annual basis. The calibration should be corrected, if the observed error exceeds 0.1 kg.

- It is NOT a requirement for all TEDDY clinical sites to use the same equipment.
- Infant scales were used until the child was able to do a standing weight measurement.

Infant:

1. Infant should be weighted without most of the clothes (light shirt) and without diaper or with scale tared to a dry diaper.
2. The scale is to be covered with only a clean paper shield and tared before placing infant on it.
3. Primary caregiver should place child in the position most comfortable for the child, sitting upright or lying supine. Ensure the infant is placed in the center of the scale and that all body parts are in the scale tray field. While baby is moving minimally, slide the scale weights to the point the beam balances at mid-point on trig loop. If using a digital scale; measurement is recorded when scale displays final weight.

4. Read measurement to the nearest 0.01 kg or the most accurate decimal point your scale allows and document the weight in kilograms on the Physical Examination Form.

   NOTE: Only weights measured specifically for TEDDY should be indicated on the Physical Exam Form; weights measured at regular health care provider visits should be indicated on the TEDDY Book extraction form. Weights entered on the Physical Exam Form can be completed +/- 30 days from the date of the TEDDY visit to allow for Long-Distance Protocol measurements, satellite site measurements, etc.

Child:

1. Child weight will be measured on a calibrated digital or beam scale.
2. Child should be wearing light clothing and must take shoes off before standing on scale. As child ages, pockets should be emptied.
3. Scale is to be tared.
4. Have child step onto weighing platform, making sure feet are positioned directly in the middle of the platform. Weight is to be distributed evenly on both feet since standing off-center may affect the measurement. The child should stand quietly with arms at the side until a steady weight is displayed on the digital scale or the beam is centered without any movement on beam scale.
5. Read the weight to the nearest 0.01 kg and document on the Physical Examination Form.

   NOTE: Only weights measured specifically for TEDDY should be indicated on the Physical Exam Form; weights measured at regular health care provider visits should be indicated on the TEDDY Book extraction form.

13.4. BIA Measurement Using TANITA Body Composition Device

Rationale

The Accelerator and Overload hypotheses have been put forward by Wilkin (2001) and Dahlquist et al (2006) as etiological models for type 1 diabetes (T1D). There is evidence that increased height and/or weight gain may have a role in the etiology of T1D, but no information is available whether the amount or distribution of body fat could play a role in the etiology of T1D. Availability of body fat measurement would increase the usability of the rich data on dietary, psychosocial and other covariates of obesity that is being collected in TEDDY. We could better analyze factors affecting the development of overweight and obesity with the addition of a body fat measurement.

The TEDDY working group on body composition measurement considered carefully different body fat measures possible in large scale epidemiological studies in relation to validity, economic costs, training effort, burden on children, families and study protocol, equipment, and availability of reference values. Waist circumference (WC) and bioelectrical impedance assessment (BIA) were considered the most relevant options. DEXA is the golden standard for body composition measurement but cannot be done in a large epidemiological study such as TEDDY.

BIA foot/foot was considered more feasible than WC, because:

- Foot-to foot BIA would be culturally appropriate, and fairly quick and need least training
- Foot-to-foot can be performed in conjunction with the weight if the current clinic scales are replaced with the new equipment
- There are BIA foot-to-foot models for children specifically
- The importance of fasting and exercise restrictions before BIA measurement would be optimal, but not necessary
- Waist circumference is not suggested to be added to the protocol, as there are concerns about the convenience for children as well as about standardization of the measurements between measurers
- Identification of waist of the child is a considerable challenge. Training for waist is not simple; it can be done but it is burdensome and quality control procedures are needed.
- BIA gives more personal space and is thus more attractive than waist circumference where you need to touch the child. BIA training is more straightforward that skinfold training.

TEDDY will use the Tanita DC-430U device to perform BIA measurement in all the TEDDY children at all age groups.

Bioelectrical Impedance Assessment (BIA)	
Equipment	Foot-to-foot
Economic costs	~$3,300 / device
Training effort	Baseline + annual repetition.
Burden - study protocol	Performance 30 sec – 1 min
Burden – children, families	Noninvasive, the currency is too low to be felt. No scientific data found on potential psychological burden
Validity	One foot/foot study in children showed excellent test-retest reliability, moderately strong absolute agreement with DEXA, and high specificity (but not sensitivity) for overfat and obese classification." (Kabiri et al. 2015)
Availability of reference values	US 8-17y (ProjectBeat, Mueller et al. 2004 – In NHANES, DXA and skinfolds); Germany 3-16y (Plachta-Danielzik et al. 2012); Sweden and Finland NA

Additional technical details can be found in the TanitaDC-430U Manual available on the TEDDY website MOO section.

Tanita Device Distribution

The DCC will order the BIA devices according to the pre-approved quantity for each clinic:

- Colorado = 2 devices
- Augusta, Georgia = 1 device
- Atlanta, Georgia = 2 devices
- Gainesville, Florida = 0 devices
- Washington = 3 devices
- Germany = 1 device
- Finland = 9 devices
- Sweden = 6 devices

Note: the back-up device for Europe is in Turku, Finland and the back-up device for the US is in Augusta, Georgia.

Data Collection Overview

1. BIA measurement will be collected at each TEDDY visit.
2. Each center has determined the number of devices needed to achieve the most repeat measurements on a majority of their cohort (including some satellite clinics).
3. Validation period: Each center should perform duplicate measurements with their existing scales and the Tanita device on 100 children **OR** for a 3 month period of time. This will provide documentation for consistency between our measurement methods.

   NOTE: Finland will continue to use their historical undressed measurements on their existing equipment and then use light clothing as per the MOO for their duplicate BIA measurement.

4. Measurements
   - Staff should stand clear of the subject during measurement to ensure accuracy.
   - Bare feet should be placed correctly on the electrode platform.
   - The correct positioning of the feet allows contact on all 4 electrode surfaces. See picture in the Body Composition Analyzer DC430-U Instruction Manual, page 16.
   - Make sure the soles of feet are free of excess dirt, as this may block the mild electric current.
   - Place arms straight down during measurement.
5. Satellite Clinic Use
   - Unplug the AC cord from the equipment when moving it.
   - Tighten the adjustable feet when moving the equipment.

Operation of the Tanita DC-430U device

Settings/Set Up

1. The electrode pad and control box are connected by a cord inside the travel bag. Be sure to carefully take both out at the same time to avoid putting any strain or pull on the connection points. Place on a solid flat surface.
2. Plug the wall plug into the wall and cylindrical end in the lower backside of the control box. **DO NOT USE A MULTI-PLUG ADAPTER.**
3. Place an SD card in the SD card slot on the right hand side of the control box. While the SD card is placed in the control box, data will be saved to the SD card and put into an excel spreadsheet format. When the device is on, an SD icon will appear in the upper left hand corner of the control box. **Note: There is no SD card included; you will have to obtain and use your own.**

4. Press the "On/Off" button.
5. The screen automatically says "PT 0.0 LB". Check the settings on the control box to make sure the correct settings are ready (Pg. 13 in the manual). **If there is no paper, hit CE to clear the P-End error.**
6. Programming Settings: **(See lettered diagram below)**
    a. **Print-outs will not be used for TEDDY subjects.**
    b. TURN ON the subject ID number so that the data for each subject can be stored on the SD card.
    c. SELECT **One Step Flow** – using this mode allows all information needed to be entered into the machine, before having the subject step on to be measured.

    Using this mode also limits the amount of time the subject needs to be on the electrode pad.

d. Use this setting to turn off the option for Athletic Mode. According to the manual, this mode is for people 18 years and older who participate in a minimum of 12 hours of cardiovascular exercise a week.

e. TEDDY uses the metric system, but the default setting is imperial.

f. The SD card allows for subject data to be stored on the memory card and saved as an excel spreadsheet with all the information. It would allow us to store a lot of data without using a large amount of memory storage. The SD card will serve as QA for each site and will be stored locally.

7. Press the "Mode Setting" button. The control box will display as "Set 00". Enter the number on the far left of the setting you would like to change and press the "Enter" button.

8. The current setting will be blinking. This is either a 1 or 0. Change to the preferred setting.

   a. Ex. We want to change setting 7 to turn the subject ID on:
   Mode Setting→7→Enter→1→Enter The ID setting is now on.

9. Go through numbers 1-23, checking the settings. Page 13 of the manual tells you what the default is, as well as your options to change those settings.

10. Once all the settings have been checked and changed to the appropriate settings, press the "Mode Setting" button one more time to get back to the main display.

Recommended Settings (One step flow)

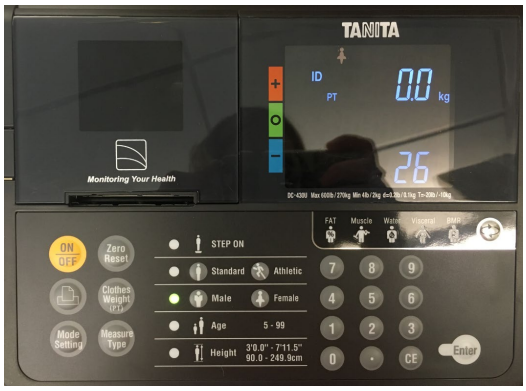
1. Turn the machine on using the "On/Off" button once the machine has been plugged in.

2. When the screen automatically says "PT 0.0 kg", then press "Enter".

3. The subject ID screen is now displayed. Enter the subject's ID number using the key pad and press "Enter".

4. Select the appropriate sex for the subject by pressing the “Male” or “Female”.

5. Enter the whole year age of the subject using the key pad and press “Enter”.



6. Enter the subject’s height in centimeters from our TEDDY height measurement (it allows us to enter to the .1) and press “Enter”.

7. "88888 kg" will blink until the machine is ready for use. Then the control box displays "Step On", prompting for the subject to get on the electrode pads. **The feet should make contact on all 4 electrode surfaces.**

8. The subject will then be measured for the body composition data. The process is complete once there is a beep and the weight in kilograms, kilograms of body fat, and body fat % is displayed on the control box.

9. Record the kilogram weight (the first number displayed) and the kilograms of body fat (the second number displayed) on the TEDDY Physical Exam form.

10. Clean the electrode pads with a non-corrosive disinfectant after each subject. Alcohol pads are sufficient.

Data Management

BIA measurements will be recorded on the Physical Exam Form as below:

2) Tanita scale measurements; follow instructions for using machine listed in the TEDDY MOO

a) Tanita scale weight ☐☐☐.☐☐ kilograms

b) Tanita scale kilograms of body fat ☐☐☐.☐☐ kilograms

☐ Tanita machine not available

☐ Parent/child refused

Note: During the initial validation period, the standard weight method will continue to be recorded on the Physical Exam Form.

Calibration/Maintenance

Each site will have an internal method of calibrating multiple machines.

- For centers/sites with only 1 device, either using standard weights (kettle bells, water bottles) or a standard person; machines should be tested monthly.
- For those centers/sites with more than 1 device, internal comparison to assess need for calibration: each site/clinical center should measure the same person on the same day, on each of their machines for kg. body fat to assess agreement between machines.

- Establish the criteria/range for being considered consistent, e.g. within +/- 0.1 kg. for any comparison Machine 1 to 2, 2 to 3, 1 to 3 (for those clinical that have 3 machines).
- Monthly calibration should be logged. (Reference D)

TANITA recommends that each facility conduct periodic checks of each unit.

Check the following at least daily:
- The unit is on a stable and level surface on a firm flooring, not on a thick carpet.
- Date and time settings.

Visually inspect the following at least weekly:
- The display for any damage or contamination
- All cables, cords, and connector ends for damage or contamination
- All safety-related labeling for legibility
- All accessories (electrodes, etc.) for wear or damage

Visually inspect the following at least monthly:
- • Mounting screws on stand
  - Continually monitor both the subject and the equipment for anomalies. If an anomaly in the subject or equipment is discovered, take appropriate action, such as stopping the equipment, while ensuring the safety of the subject.
  - Do not lean against the equipment.

Troubleshooting Error Messages – See the Body Composition Analyzer DC430-U Instruction Manual, page 31.

Frequently Asked Questions

1. **Is there a way to blind the display so that the subjects can't see the Body Fat % that is displayed after the measurement has been done?** There is no way to programmatically blind the display, but the display box can be arranged so that it is positioned on a shelf or countertop away from view of the person being measured.

2. **Do we want to utilize the SD card option for data storage?** See item 6. F above.

3. **Would there be a way to setup an output file from the excel spreadsheet that is generated by/from the SD card?** Below is an example of a portion of the excel file from the SD card. Each site will store this locally and create a file naming convention. The ID entered is the subject's Local Code. Entering the biological age at the visit identifies which visit is being recorded on the SD card.

MACHINE	ID	STATUS	MDATE	MTIME	BODY	GENDER	AGE	HEIGHT	PT kg	WEIGHT kg	FATPER
DC-430	0000000000111111	0	7/20/2016	10:41:34	0	1	5	115.8	0	21.2	20.6
DC-430	0000000000252590	0	7/20/2016	10:36:35	0	1	8	154.3	0	30.4	7
DC-430	0000000000235111	0	7/20/2016	11:10:27	0	2	8	127.5	0	28.9	27.3
DC-430	0000000000189953	0	7/11/2016	8:27:10	0	2	9	133	0	27.7	19.3
DC-430	0000000000189949	0	7/20/2016	12:13:22	0	1	9	136	0	41	36.9
DC-430	0000000000111111	0	7/20/2016	10:38:32	0	2	10	153.2	0	48.3	26

4. **What is the expected validation period before switching to measurements using only the Tanita device?** The Clinical Implementation Committee requests each site perform duplicate measurements with existing scales and the Tanita device on 100 children OR for a 3 month period of time.

5. **What is the best way to address general body image concerns?** Emphasize that this is just RAW data.

6. **What kinds of questions should we expect from the families?**
   - **Can we all get measured?** Each center will develop the best response for this question considering the additional time and the impact on the clinic schedule. The use of a fake ID number such as 999999 is recommended instead of removal and replacement of the SD card.
     NOTE: This equipment must not be used on subjects with pacemakers or other mechanical implants. This equipment passes a weak electrical current through the body which could interfere with and cause the malfunction of electrical medical implants, resulting in serious harm.
   - **Is the electrical signal safe?** It's a very low, safe electrical signal. **Do I have to take off my socks?** Yes,use the regular scale for children who balk at removing their socks.

Reference A

Operation on Default Settings (Two step flow) to be used if needed. One-step flow is the standard for TEDDY centers.

1. Turn the machine on using the "On/Off" button once the machine has been plugged in.
2. The screen automatically says "PT 0.0 LB", prompting for the clothes weight to be removed from the total weight of the subject. Once the clothes weight is entered (if we choose to use this option) using the number pad on the control box, press "Enter".
3. "88888 LB" will blink until the machine is ready for use. Then the control box displays "Step On", prompting for the subject to get on the electrode pads. Be sure the heel and ball of the foot is on the center of the pads. If the subject has smaller feet, the ball of the foot and heel must be touching the edges of the electrode plate. THE SUBJECT SHOULD REMAIN ON THE ELECTRODE PLATE.
4. Once the machine has locked the weight a, "Body Type" is to be selected either from "Standard" or "Athletic". Select "Standard" using the key pad.
5. Select the appropriate sex for the subject by pressing the "Male" or "Female".
6. Enter the age of the subject using the key pad and press "Enter". It only allows whole years to be entered, so we can't differentiate for the half year visits.
7. Enter the subject's height in feet and inches from our TEDDY height measurement (it allows us to enter up to .1) and press "Enter".

8. The subject will then be measured for the body composition data. The process is complete once there is a beep and the weight, pounds of body fat, and body fat % is displayed on the control box. **Note: Results for children (ages 5-17) include weight, fat, and BMI. Results for adults include weight, fat, muscle, bone, bone mass and BMI.**
9. Clean the electrode pads with a non-corrosive disinfectant after each subject. There is simply no maintenance other than the use of alcohol to wipe the foot pads clean and glass cleaner to keep them shiny-always apply to a cloth first and then to the product; avoid soaps.

Reference B

Operation for weight only measurement

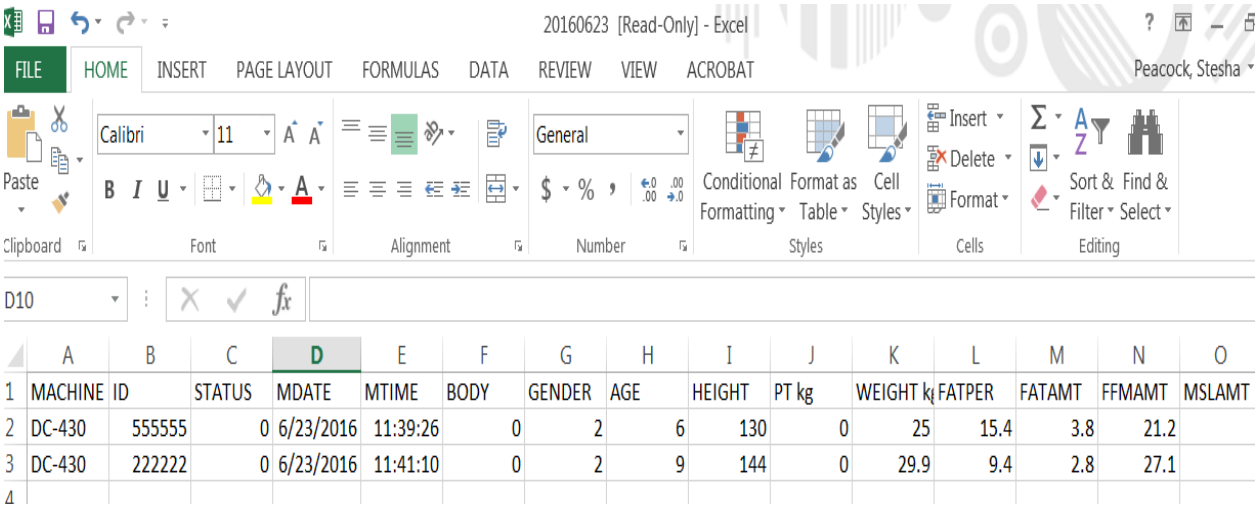
1. Turn the machine on using the "On/Off" button once the machine has been plugged in.
2. The screen automatically says "PT 0.0 LB", prompting for the clothes weight to be removed from the total weight of the subject.
3. Press the "Measure Type" button. A large symbol will appear in the center of the display indicating a weight.
4. The subject ID screen is now displayed. Enter the subject's ID number using the key pad and press "Enter".
5. "88888 kg" will blink until the machine is ready for use. Then the control box displays "Step On", prompting for the subject to get on the electrode pads.
6. The process is complete once there is a beep and the weight is displayed on the control box.

Reference C

Retrieving SD Card Data

1. Once the data has been collected, remove the SD card from the right side of the control box.
2. Place the SD card in a card reader.
3. Place the card reader in the USB port on the computer.
4. Open the Drive and click on the TANITA folder.
5. The folder contains spreadsheets for each day of data collection and is stored as YEARMONTHDAY → 20160623.

6. Open the desired spreadsheet and all of each day's data has been saved. We can find the correct subject based on ID and get the correct information for each subject.



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
1	MACHINE	ID	STATUS	MDATE	MTIME	BODY	GENDER	AGE	HEIGHT	PT kg	WEIGHT k	FATPER	FATAMT	FFMAMT	MSLAMT
2	DC-430	555555	0	6/23/2016	11:39:26	0	2	6	130	0	25	15.4	3.8	21.2	
3	DC-430	222222	0	6/23/2016	11:41:10	0	2	9	144	0	29.9	9.4	2.8	27.1	
4															

Reference D

Tanita BIA Device Internal Calibration Log

	Date	Machine 1 - Weight Kg/Fat Kg.	Machine 2 - Weight Kg/Fat Kg.	Machine 3 - – Weight Kg/Fat Kg.	Staff ID
January					
February					
March					
April					
May					
June					
July					
August					
September					

October					
November					
December					

13.5. Blood Samples

Venous blood will be drawn for processing into serum, plasma, erythrocytes, PBMCs, buffy coats (for subjects where it is not possible to isolate and freeze living PBMC, the cells will be harvested and frozen as a buffy coat sample.) and mRNA. If venous blood is not available, capillary blood will be drawn.

Optimal blood volumes to be drawn at each clinic visit are listed below (Table 13.1). The volumes reflect both the scientific needs of the study and the experience of the TEDDY clinical centers.

Table 13.1 Optimal Blood Volumes at Each Clinic Visit

Clinic Visit	Optimal Total Blood Volume
3 month	6.5 ml
6 month	8.5 ml
9 month	11.5 ml
12 month	16.5 ml
15 month	16.5 ml
18 month	16.5 ml
21 - 33 months	20.5 ml
>36 months	At least 25.5 ml; as children get older additional blood volume will be collected based upon local IRB/Ethics Board approval and the weight of the child. At no time will the blood draw volume exceed what is allowable according to the subject's body weight - 3 mL/kg per visit
48 month	30.5 ml

In cases where the optimal blood volume is not available, the priorities for the blood samples are shown in the following tables.

NOTE: It has been decided that the HbA1c sample will be the second priority following the SST.

*For blood volumes of 4 ml or less, use a 4 ml CPT tube. For samples of greater than 4 ml, use an 8 ml CPT tube. For blood volumes of less than 2 ml, do not isolate PBMC or buffy coat.

**Remove reagent from the ABI Tempus tube so that remaining reagent volume is twice that of blood volume that will be added.

Table 13.2 Three Month Aliquoting Priority List

Blood Volume	SST Tube	CPT Tube	ABI Tube
<1.5 ml	0.5 ml	Remainder*	0
1.5 ml	0.5 ml	1.0 ml*	0
2.0 ml	0.7 ml	1.3 ml*	0
3.0 ml	1.0 ml	2.0 ml	0
4.0 ml	1.5 ml	2.5 ml	0
5.0 ml	1.5 ml	2.5 ml	1.0 ml**
6.0 ml	1.5 ml	3.0 ml	1.5ml**
6.5 ml	1.5 ml	3.0 ml	2.0 ml

Table 13.3 Six Month Aliquoting Priority List

Blood Volume	SST Tube	CPT Tube	ABI Tube
<1.5 ml	0.5 ml	Remainder*	0
1.5 ml	0.5 ml	1.0 ml*	0
2.0 ml	0.7 ml	1.3 ml*	0
3.0 ml	1.0 ml	2.0 ml	0
4.0 ml	1.5 ml	2.5 ml	0
5.0 ml	1.5 ml	2.5 ml	1.0 ml**
6.0 ml	1.5 ml	3.0 ml	1.5 ml**
6.5 ml	1.5 ml	3.0 ml	2.0 ml
7.0 ml	1.5 ml	3.5 ml	2.0 ml
8.0 ml	2.0 ml	3.5 ml	2.5 ml
8.5 ml	2.0 ml	4.0 ml	2.5 ml

Table 13.4 Nine Month Aliquoting Priority List

Blood Volume	SST Tube	CPT Tube	ABI Tube	EDTA Tube
<1.5 ml	0.5 ml	Remainder*	0	0
1.5 ml	0.5 ml	1.0 ml*	0	0
2.0 ml	0.7 ml	1.3 ml*	0	0
3.0 ml	1.0 ml	2.0 ml	0	0
4.0 ml	1.5 ml	2.5 ml	0	0
5.0 ml	1.5 ml	2.5 ml	1.0 ml**	0
6.0 ml	1.5 ml	3.0 ml	1.5 ml**	0
6.5 ml	1.5 ml	3.0 ml	2.0 ml	0
7.0 ml	1.5 ml	3.5 ml	2.0 ml	0
8.0 ml	2.0 ml	3.5 ml	2.5 ml	0
8.5 ml	2.0 ml	3.5 ml	2.0 ml	1.0 ml
9.0 ml	2.0 ml	3.5 ml	2.5 ml	1.0 ml
9.5 ml	2.0 ml	4.0 ml	2.5 ml	1.0 ml
10.0 ml	2.5 ml	4.0 ml	2.5 ml	1.0 ml
10.5 ml	2.5 ml	4.5 ml	2.5 ml	1.0 ml
11.0 ml	2.5 ml	5.0 ml	2.5 ml	1.0 ml
11.5 ml	3.0 ml	5.0 ml	2.5 ml	1.0 ml

Table 13.5 Twelve, Fifteen and Eighteen month Aliquoting Priority List

Blood Volume	SST Tube	CPT Tube	ABI Tube	EDTA Tube
<1.5 ml	0.5 ml	Remainder*	0	0
1.5 ml	0.5 ml	1.0 ml*	0	0
2.0 ml	0.7 ml	1.3 ml*	0	0
3.0 ml	1.0 ml	2.0 ml	0	0
4.0 ml	1.5 ml	2.5 ml	0	0
5.0 ml	1.5 ml	2.5 ml	1.0 ml**	0
6.0 ml	1.5 ml	3.0 ml	1.5 ml**	0
6.5 ml	1.5 ml	3.0 ml	2.0 ml	0
7.0 ml	1.5 ml	3.5 ml	2.0 ml	0
8.0 ml	2.0 ml	3.5 ml	2.5 ml	0
8.5 ml	2.0 ml	3.5 ml	2.0 ml	1.0 ml***
9.0 ml	2.0 ml	3.5 ml	2.5 ml	1.0 ml***
9.5 ml	2.0 ml	4.0 ml	2.5 ml	1.0 ml***
10.0 ml	2.5 ml	4.0 ml	2.5 ml	1.0 ml***
10.5 ml	2.5 ml	4.5 ml	2.5 ml	1.0 ml***
11.0 ml	2.5 ml	5.0 ml	2.5 ml	1.0 ml***
12.0 ml	3.0 ml	5.5 ml	2.5 ml	1.0 ml***
13.0 ml	3.5 ml	6.0 ml	2.5 ml	1.0 ml***
14.0 ml	4.0 ml	6.5 ml	2.5 ml	1.0 ml***
15.0 ml	4.5 ml	7.0 ml	2.5 ml	1.0 ml***
16.5 ml	5.0 ml	8.0 ml	2.5 ml	1.0 ml***

***EDTA tube for HLA confirmation drawn at 12 or 15 month visit (or at next scheduled visit) if not collected yet and if adequate overall blood volume achieved at the visit as indicated. The HLA confirmation sample can be collected outside the sample window. If already collected, do not recollect but add 1 ml to CPT tube volume.

Table 13.6 21 – 33 months Aliquoting Priority List

Blood Volume	SST Tube	CPT Tube	ABI Tube
<1.5 ml	0.5 ml	Remainder*	0
1.5 ml	0.5 ml	1.0 ml*	0
2.0 ml	0.7 ml	1.3 ml*	0
3.0 ml	1.0 ml	2.0 ml	0
4.0 ml	1.5 ml	2.5 ml	0
5.0 ml	1.5 ml	2.5 ml	1.0 ml**
6.0 ml	1.5 ml	3.0 ml	1.5 ml**
6.5 ml	1.5 ml	3.0 ml	2.0 ml
7.0 ml	1.5 ml	3.5 ml	2.0 ml
8.0 ml	2.0 ml	3.5 ml	2.5 ml
8.5 ml	2.0 ml	4.5 ml	2.0 ml
9.0 ml	2.0 ml	4.5 ml	2.5 ml
9.5 ml	2.0 ml	5.0 ml	2.5 ml
10.0 ml	2.5 ml	5.0 ml	2.5 ml
10.5 ml	2.5 ml	5.5 ml	2.5 ml
11.0 ml	2.5 ml	6.0 ml	2.5 ml
12.0 ml	3.0 ml	6.5 ml	2.5 ml
13.0 ml	3.5 ml	7.0 ml	2.5 ml
14.0 ml	4.0 ml	7.5 ml	2.5 ml
15.0 ml	4.5 ml	8.0 ml	2.5 ml
16.0 ml	4.5 ml	9.0 ml	2.5 ml
17.0 ml	5.0 ml	9.5 ml	2.5 ml
18.0 ml	5.5 ml	10.0 ml	2.5 ml
19.0 ml	6.0 ml	10.5 ml	2.5 ml
20.5 ml	6.5 ml	11.5 ml	2.5 ml

Table 13.7 36 – 45 months, 51 months – 15 years# Aliquoting Priority List

Blood Volume	SST Tube	CPT Tube	ABI Tube
<1.5 ml	0.5 ml	Remainder*	0
1.5 ml	0.5 ml	1.0 ml*	0
2.0 ml	0.7 ml	1.3 ml*	0
3.0 ml	1.0 ml	2.0 ml	0
4.0 ml	1.5 ml	2.5 ml	0
5.0 ml	1.5 ml	2.5 ml	1.0 ml**
6.0 ml	1.5 ml	3.0 ml	1.5 ml**
6.5 ml	1.5 ml	3.0 ml	2.0 ml
7.0 ml	1.5 ml	3.5 ml	2.0 ml
8.0 ml	2.0 ml	3.5 ml	2.5 ml

8.5 ml	2.0 ml	4.5 ml	2.0 ml
9.0 ml	2.0 ml	4.5 ml	2.5 ml
9.5 ml	2.0 ml	5.0 ml	2.5 ml
10.0 ml	2.5 ml	5.0 ml	2.5 ml
10.5 ml	2.5 ml	5.5 ml	2.5 ml
11.0 ml	2.5 ml	6.0 ml	2.5 ml
12.0 ml	3.0 ml	6.5 ml	2.5 ml
13.0 ml	3.5 ml	7.0 ml	2.5 ml
14.0 ml	4.0 ml	7.5 ml	2.5 ml
15.0 ml	4.5 ml	8.0 ml	2.5 ml
16.0 ml	4.5 ml	9.0 ml	2.5 ml
17.0 ml	5.0 ml	9.5 ml	2.5 ml
18.0 ml	5.5 ml	10.0 ml	2.5 ml
19.0 ml	6.0 ml	10.5 ml	2.5 ml
20.5 ml	6.5 ml	11.5 ml	2.5 ml
21.5 ml	7.5 ml	11.5 ml	2.5 ml
22.5 ml	7.5 ml	12.5 ml	2.5 ml
23.5 ml	7.5 ml	13.5 ml	2.5 ml
24.5 ml	7.5 ml	14.5 ml	2.5 ml
25.5 ml	7.5 ml	15.5 ml	2.5 ml
26.5 ml^	8.0 ml	16.0 ml	2.5 ml
27.5 ml^	9.0 ml	16.0 ml	2.5 ml
28.5 ml^	10.0 ml	16.0 ml	2.5 ml
29.5 ml^	11.0 ml	16.0 ml	2.5 ml
30.5 ml^	12.0 ml	16.0 ml	2.5 ml
31.5 ml^	13.0 ml	16.0 ml	2.5 ml
32.5 ml^	10.0 ml	20.0 ml	2.5 ml
33.5 ml^	11.0 ml	20.0 ml	2.5 ml
34.5 ml^	12.0 ml	20.0 ml	2.5 ml
35.5 ml^	13.0 ml	20.0 ml	2.5 ml
36.5 ml^	10.0 ml	24.0 ml	2.5 ml
37.5 ml^	11.0 ml	24.0 ml	2.5 ml
38.5 ml^	12.0 ml	24.0 ml	2.5 ml
39.5 ml^	13.0 ml	24.0 ml	2.5 ml
40.5 ml^	14.0 ml	24.0 ml	2.5 ml
41.5 ml^	15.0 ml	24.0 ml	2.5 ml
42.5 ml^	16.0 ml	24.0 ml	2.5 ml
43.5 ml^	17.0 ml	24.0 ml	2.5 ml
44.5 ml^	18.0 ml	24.0 ml	2.5 ml
45.5 ml^	19.0 ml	24.0 ml	2.5 ml
46.5 ml^	20.0 ml	24.0 ml	2.5 ml
47.5 ml^	21.0 ml	24.0 ml	2.5 ml

= Children four years of age and older who have been deemed persistent autoantibody positive will remain on the three month visit schedule (confirmation results from the confirmatory

Autoantibody lab will not be taken into consideration for determining the subject's visit schedule, only the local lab's results will be used for this); all other subjects will attend biannual clinic visits beginning at 4 years of age until age 15. For subjects who become autoantibody positive at 4 years of age or older, the subject will be reinstated on the three month visit schedule at the first indication of autoantibody positivity and will stay on if persistent. If the next available sample is negative, thus the subject is not deemed persistent autoantibody positive, the subject will be seen every six months instead of every three months from that point on. Subjects who have been persistently single autoantibody positive, but who become negative to all autoantibodies for 1 year or more will be placed on the biannual visit schedule after 4 years of age. Subjects who have been persistently multiple autoantibody positive, but who become negative to all antibodies for 1 year or more will remain on the three month visit schedule.

^ = as children get older additional blood volume will be collected based upon local IRB/Ethics Board approval and the weight of the child. At no time will the blood draw volume exceed what is allowable according to the subject's body weight - 3 mL/kg per visit.

- 0.5 ml HbA1c samples can be taken from SST volumes in accordance with TEDDY Protocol.
- If an OGTT is scheduled at the same time as the regular visit, 3 ml can be taken from SST and CPT tube volumes.
- At the 6 year visit or later when the 2 ml Whole Blood Storage Sample is collected, 1 ml can be subtracted from the designated SST tube volume and 1 ml can be subtracted from the designated CPT tube volume.

Table 13.8 48 Month Aliquoting Priority List

Blood Volume	SST Tube	CPT Tube	ABI Tube	EDTA Tube
<1.5 ml	0.5 ml	Remainder*	0	0
1.5 ml	0.5 ml	1.0 ml*	0	0
2.0 ml	0.7 ml	1.3 ml*	0	0
3.0 ml	1.0 ml	2.0 ml	0	0
4.0 ml	1.5 ml	2.5 ml	0	0
5.0 ml	1.5 ml	2.5 ml	1.0 ml**	0
6.0 ml	1.5 ml	3.0 ml	1.5 ml**	0
6.5 ml	1.5 ml	3.0 ml	2.0 ml	0
7.0 ml	1.5 ml	3.5 ml	2.0 ml	0
8.0 ml	2.0 ml	3.5 ml	2.5 ml	0
8.5 ml	2.0 ml	4.5 ml	2.0 ml	0
9.0 ml	2.0 ml	4.5 ml	2.5 ml	0
9.5 ml	2.0 ml	5.0 ml	2.5 ml	0
10.0 ml	2.5 ml	5.0 ml	2.5 ml	0
10.5 ml	2.5 ml	5.5 ml	2.5 ml	0
11.0 ml	2.5 ml	6.0 ml	2.5 ml	0
12.0 ml	3.0 ml	6.5 ml	2.5 ml	0
13.0 ml	3.5 ml	7.0 ml	2.5 ml	0
14.0 ml	4.0 ml	7.5 ml	2.5 ml	0
15.0 ml	4.5 ml	8.0 ml	2.5 ml	0

16.0 ml	5.5 ml	8.0 ml	2.5 ml	0
17.0 ml	5.5 ml	9.0 ml	2.5 ml	0
18.0 ml	4.0 ml	6.5 ml	2.5 ml	5 ml ****
19.0 ml	4.5 ml	7.0 ml	2.5 ml	5 ml ****
20.5 ml	5.0 ml	8.0 ml	2.5 ml	5 ml ****
21.5 ml	5.5 ml	8.5 ml	2.5 ml	5 ml ****
22.5 ml	5.5 ml	9.5 ml	2.5 ml	5 ml ****
23.5 ml	6.0 ml	10.0 ml	2.5 ml	5 ml ****
24.5 ml	6.0 ml	11.0 ml	2.5 ml	5 ml ****
25.5 ml	6.5 ml	11.5 ml	2.5 ml	5 ml ****
26.5 ml	7.5 ml	11.5 ml	2.5 ml	5 ml ****
27.5 ml	7.5 ml	12.5 ml	2.5 ml	5 ml ****
28.5 ml	7.5 ml	13.5 ml	2.5 ml	5 ml ****
29.5 ml	7.5 ml	14.5 ml	2.5 ml	5 ml ****
30.5 ml	7.5 ml	15.5 ml	2.5 ml	5 ml ****

****If overall blood volume is insufficient at the 48 month visit for collection of the 5 ml EDTA sample for non-HLA genetics, then it may instead be collected at the 54 month, 60 month, 66 month or 69 month visit. For whichever single visit includes the 5 ml EDTA sample, use Table 13.7 and for all other visits at age 21 months or older, use Table 13.6. The 5 ml non-HLA sample should be collected as soon as possible and can be collected outside the sample window.

Serum is the primary objective. The first primary endpoint is to measure insulin, GAD65 and IA-2 (ICA512) autoantibodies. The minimum volume to analyze all three autoantibodies is 100 microliters of serum.

13.5.1. Venous Blood Draw

The blood drawing procedure is usually the most uncomfortable and stressful part of the clinic visit for all parties involved. It is recommended that the timing of this event take place after all other data collection is complete. Whereas it is important for all clinical staff to be proficient and feel comfortable with performing the procedure on all age groups in TEDDY's pediatric population, there is no guarantee that the visit will go as planned. If two attempts at venous access are made without an adequate sample, heel sticks (not recommended after 12 months of age) or finger pricks for capillary blood may be done (see Section below on Capillary Blood Draw) as long as the stress level of parents and child are assessed beforehand. While it is the goal to obtain the blood, it is imperative that the experience be a positive one for all.

Use of EMLA cream can minimize the discomfort of the blood draw. Common venipuncture sites for infants and children include the antecubital area, dorsal portion of hands, and the lateral foot for infants. Careful evaluation of potential sites is critical. EMLA cream is to be applied 45-60 minutes prior to the procedure. EMLA cream is to be applied to intact skin with an occlusive dressing.

Children with darker pigmented skin may need additional time for EMLA to produce anesthesia. Multiple sites can be prepared to allow greater flexibility for site selection, but no more than 2 attempts for the blood draw are permitted. It is important to follow the given dosage guidelines for EMLA administration with no more than 4 sites being prepared

Table 13.9 EMLA Maximum Recommended Dose, Application Area and Application Time by Age and Weight

Age/weight requirements	Total dose	Max. surface area	Max. application time
0-3 mo. < 5kg	1g	10cm	1 hour
3-12 mo. >5kg	2g	20cm	4 hours
> 1 year and > 10 kg	10g	100cm	10 hours

The use of heating pads and heel warmers will promote venous selection.

Allowing the child to choose a special bandage allows them to feel more in control and promotes a positive aspect of the blood draw.

Procedure explanation:
Preparing a child and their parent/primary caretaker can help reduce everyone's anxiety and precipitate a successful procedure. Allow adequate time to prepare the child; however do not delay the procedure.

- Allowing the child to repeatedly delay the procedure (to be "ready") will only increase their anxiety.
- Use age-appropriate and simple words to explain the procedure.
- Explain each step of the procedure to the child and the parent so everyone knows what is expected and encourages cooperation.
- Children may want to talk about their fears and should be encouraged to ask questions.
- Tell the child what to expect, children often imagine worse things than what actually happens.
- Children are less likely to resist if prepared.
- Parent's displaying a positive attitude toward procedures will alleviate anxiety for the child, it may be necessary for staff to guide parents in showing a positive attitude.
- Consider the child's attention span. Don't talk too long.
- Be clear. Explain that "taking blood" does not mean taking all of the blood, but only a little.
- Be honest, it might hurt.
- Give the child permission to cry or yell if needed. Give the child suggestions for how to maintain control, such as counting, deep breathing, or thinking about a relaxing place.

Positioning

During the blood draw procedure it is important to position the child to facilitate a comfortable technique for the staff while allowing a sense of security for the child and preventing injury.

- Care must be taken to properly position the child to prevent injuries. The child must be held firmly but gently with joints (shoulder/hip) in a neutral position to prevent a dislocation or nursemaids elbow.
- Allow the child to sit on a parent/primary caretaker's lap for procedures or to lie on a cushioned surface with the parent positioned directly over the child. The parent can gently yet firmly restrain the child. Adequate clinical staff should be utilized at all time for procedures, i.e., for phlebotomy procedures, child sits on parents lap, one staff holds the child's arm, the nurse/phlebotomist draws the blood.

Children should never be controlled using external restraints.

Equipment

a. EMLA cream (lidocaine 2.5%, prilocaine 2.5%) (or substitute)
b. Tegaderm occlusive dressing
c. pair of disposable latex-free gloves
d. alcohol wipes (Isopropyl alcohol 70% sterile)
e. winged infusion set or butterfly needle (21G and 23G are available) phlebotomist should use their judgment when choosing size appropriate needles for the child.
f. 5 cc or 10 cc syringe
g. tourniquet
h. 2x2 gauze
i. cotton ball
j. bandage
k. protective eye goggles or glasses
l. vacutainer holder
m. visit-specific blood collection tubes (CPT tube must be wrapped in foil for annual visits)
n. visit-specific cryovials with color cap inserts
o. test tube racks for holding vacutainer tubes and cryovials

Preparation

a. At the beginning of the visit, prepare the most optimal sites (at least two) for venipuncture with topical EMLA anesthetic cream. Optimal sites for infants and children are the antecubital veins or dorsal hand veins. Assess the child's veins and site preferences prior to applying EMLA cream.
b. Disinfect the sites with alcohol wipes and place approximately 1 cc of EMLA cream on each site.
c. Take a tegaderm occlusive dressing and remove the center cut-out piece.

d. Peel the paper liner from the paper framed dressing
e. Cover the EMLA cream so that you get a thick layer underneath. Do not spread out the cream. Smooth down the dressing edges carefully and ensure it is secure to avoid leakage.
f. Leave dressing in place for 30-40 minutes in order to provide a painless experience. NOTE: dark-skinned children require longer time for full local anesthesia
g. Remove the paper frame. The time of application can be marked on the occlusive dressing.
h. The appropriate sized syringe should be removed from sterile pull-apart package at the time of assemble only. The strategy is to collect the total volume of blood for the clinic visit into a single syringe and then use that blood-filled syringe to aliquot the exact amount of blood needed into each of the separate vacutainers listed below. At the discretion of the clinician the sample can be drawn directly into the vacutainer tubes rather than using a syringe and then aliquoting.
i. Pull plunger back on the syringe to ensure the seal is broken.
j. Connect an appropriate sized winged infusion set or butterfly to the syringe, but leave needle covered until the time of insertion. Project the amount of blood that is needed based on the weight and age of the child, and prepare syringe accordingly.

Transfer to Blood Collection Tubes

a. Serum will be collected in a SST tube (gold top tube)
b. Plasma will be collected in a CPT (blue/grey top) tube wrapped in foil to protect the sample from light
c. mRNA will be collected in an ABI (clear top) tube. The ABI tube contains 6 ml of liquid preservative to which no more than 2.5 ml of whole blood should be added.
d. Whole blood for HLA genotyping and non-HLA genotyping will be collected in an EDTA (lavender top) tube. The HLA genotyping sample will be drawn from subjects at the 6, 9 12 or 15 month clinic visit. Sites are encouraged to complete this collection by the earliest visit with a full volume blood draw, but in all cases by the 15 month visit. The non-HLA genotyping sample will be drawn from subjects at 4 years of age. If the non-HLA genotyping sample cannot be collected at the 4 year visit, it should be attempted to be collected at the next scheduled visit, but must be collected by the 5 year 9 month visit. If the HLA or non-HLA genotyping sample is not collected within the window, it can still be collected later but the DCC needs to be notified.
e. 0.5 ml of whole blood for HbA1c measurement will be collected in a small EDTA tube. The HbA1c sample will be drawn at the next TEDDY visit and every visit thereafter from children who are positive at the 9 month visit or later for at least one autoantibody (regardless of autoantibody positivity confirmation or persistence). Following this logic, the first possible visit that the HbA1c sample could be collected at is the 12 month visit.

The appropriate size and number of collection tubes for each visit are detailed in the table below:

Table 13.10 Number and Size of Collection Tubes for Each Clinic Visit

Clinic Visit	SST	CPT	ABI	EDTA
3 month	1 x 2.5 ml	1 x 4 ml	1 x 10ml	
6 month	1 x 2.5 ml	1 x 4 ml	1 x 10 ml	
9 month	1 x 7 ml	1 x 8 ml	1 x 10 ml	1 x 2 ml^
12 month	1 x 7 ml	1 x 8 ml	1 x 10 ml	1 x 0.5 ml#
15 month	1 x 7 ml	1 x 8 ml	1 x 10 ml	1 x 0.5 ml#
18 month	1 x 7 ml	1 x 8 ml	1 x 10 ml	1 x 0.5 ml#
21 - 33 months	1 x 7 ml	1 x 8 ml and 1 x 4 ml	1 x 10 ml	1 x 0.5 ml#
≥36 months+	1 x 10 ml	2 x 8 ml	1 x 10 ml	1 x 0.5 ml#
4 year (48 month) visit	1 x 10 ml	2 x 8 ml	1 x 10 ml	1 x 0.5 ml#; 1 x 6 ml@

^ = The HLA genotyping sample will be drawn from subjects at the 6, 9 12 or 15 month clinic visit. Sites are encouraged to complete this collection by the earliest visit with a full volume blood draw, but in all cases by the 15 month visit. If the HLA confirmation sample is collected at the 6 month visit, only 0.5 mL of blood is required to be collected for this sample. If the HLA confirmation sample is collected at the 9, 12 or 15 month visit 1 mL of blood should be collected for this sample.

= Whole blood for HbA1c measurement will be collected in a 0.5 mL EDTA bullet tube. The HbA1c sample will be drawn at the next TEDDY visit and every visit thereafter from children who are positive at the 9 month visit or later for at least one autoantibody (regardless of autoantibody positivity confirmation or persistence).

@ = A whole blood sample will be drawn from subjects at the 4 year clinic visit for the non-HLA genotyping sample. If the sample cannot be collected at the 4 year visit, it should be attempted to be collected at the next scheduled visit, but must be collected by the 5 year 9 month visit.

+ = As children get older additional blood volume will be collected based upon local IRB/Ethics Board approval and the weight of the child. At no time will the blood draw volume exceed what is allowable according to the subject's body weight - 3 mL/kg per visit.

Age-appropriate toys

Toys can be utilized as distractions during the blood collection procedure.

Parents/primary caretakers may play with these toys near the child while clinic staff performs the venipuncture.

Toys that make noise, light up, play music are very helpful in distracting the child. Blowing bubbles can also be helpful. Distraction toys should be safe for all ages and easy to clean.

Candy for children age 2 years and older may aid with the blood draw procedure and minimize pain or discomfort.

Positive reinforcement

Clinic staff should use positive words of encouragement with the child preceding and during all procedures. It is important to let the child know they are doing a "good job" no matter what and are doing something very important of which we are all very proud.

Depending on the child's age and development, education about the study and their part in the study may be very helpful.

Procedures should never be seen as a punishment for bad behavior or threatened as such. Staff may need to guide parents to accept fear and hesitation in the child as natural anxiety.

Venipuncture Procedures

It is important to take into account age appropriate measures to ease the anxiety associated with the procedure and to accomplish a positive experience for the child, family, and clinical worker. Methods for explanation of the procedure, distraction approaches, and favorable comfort techniques must be implemented based on the subject's age group. ***Study personnel training will place special emphasis on expert pediatric venipuncture skills and sensitivity to all potential subject concerns.***

a. Approach the subject and family in a friendly, calm manner. Provide for their comfort as much as possible.
b. Explain the procedure to the subject's family.
c. Wash your hands with soap and water and put on a pair of disposable plastic latex gloves.
d. Depending on the age, have the parent or staff hold the child on their lap with one arm around the child's waist and the other hand under and clasping the child's elbow, or have the child lay down and have the parent or staff lean over the child restraining the nearest arm with their body while holding the extended arm securely or position the child directly in the blood-drawing chair.
e. Remove the occlusive dressing, wipe off the EMLA cream with gauze, and clean the entire area with an antiseptic solution. The duration of effective skin anesthesia will be at least 1 hour after removal of the occlusive dressing.
f. Make sure the participant's arm is in a flat and stable position.
g. Identify the best vein possible.

h. Once venipuncture site has been determined, apply tourniquet. If drawing from the hand, apply the tourniquet to the wrist proximal to the wrist bone and curve the hand in a secure hold. If the antecubital vein is most optimal, apply tourniquet 2 inches above site and secure entire arm. A well applied tourniquet will slow venous blood return, causing veins to distend. It will not block arterial blood supply, so pulses distal to the tourniquet should still be palpable and the limb should not blanch. PRECAUTIONS: The tourniquet should be left on the minimal amount of time necessary for an adequate amount of blood to be obtained.
i. Make certain the site extremity remains secure and still. This may involve assistance from other lab or clinical personnel. Do not underestimate the strength of a small child, or the lack of strength of the parent. It is the parent's responsibility to provide comfort or distraction to the child, not to secure the site. If there is any question, request assistance. It is important to be conscious of positioning of the arm as dislocation of the shoulder can result from poor positioning. The arm should be extended but not hyperextended from the body. The child should be restrained in such a way as to prevent their body moving forward while the arm remains to the side, never towards the back. To assist in determining if what is felt in the antecubital area is a vein verses a tendon, the hand should be rotated supine to dorsal; a vein will remain palpable in both positions whereas a tendon will only be palpable when hand is supine.
j. Cleanse venipuncture site with an alcohol wipe, using circular motion toward the periphery. Allow area to dry before proceeding. This prevents the burning sensation for patients when venipuncture is performed and it prevents hemolysis of the blood.
k. Hold the syringe attached to the butterfly in the dominant hand or lay the syringe next to the child's arm. Hold the wing portion of the needle between the thumb and the index finger while pulling the skin over the knuckles for the dorsal hand site or toward the wrist for the antecubital site. At the discretion of the clinician the sample can be drawn directly into the vacutainer tubes rather than using a syringe and then aliquoting.
l. Insert the needle at a 10 to 15 degree angle, ensuring the needle bevel is face up and parallel to the vein. Use a straight stab; do not poke around. A flash or small amount of blood will appear in the tubing when the needle is successfully in the vein.
m. Secure the needle in the vein by holding it with the thumb of the opposite hand. Slowly draw the blood in the attached syringe in a downward position, making certain that the needle remains secure.
n. When adequate blood is obtained, remove the tourniquet
o. Remove the needle quickly and immediately apply gentle pressure to the site with the gauze pad or cotton ball.
p. Activate the safety device feature on the needle to prevent an unnecessary needle stick. Remove and discard the butterfly needle set up.
q. Have the parent keep arm fully extended and elevated. Have them apply pressure over puncture site for a few minutes.

r. Check site for bleeding. If site is still bleeding, continue direct pressure. If site has stopped bleeding, apply bandage to venipuncture site.*
s. Transfer desired amount of blood into collection tubes.
t. Invert tubes to mix thoroughly, 5-10 times
u. Dispose of butterfly and other contaminated materials in sharp box, throw away materials not used, remove gloves, and wash hands.

***NOTE: If a cotton ball is used to help stop bleeding from a phlebotomy site, it should not be held in place by tape or a Band-Aid on a child less than 3 years old. Cotton balls should be held in place by an adult until bleeding from the site has stopped. Children less than 3 years old should not leave the office with a Band-Aid on the phlebotomy site unless it is requested by the parent and the risk of aspiration has been explained to the parent. An alternative to a Band-Aid is an adhesive wrap called Coban.**

13.5.2. Capillary Blood Draw

Occasionally, it may be necessary to obtain a blood sample by other methods than a venous blood draw. Either a heel stick, for infants, or a finger stick, for ambulating children, may be used to obtain a quality blood specimen, although the venous blood draw is the preferred method.

13.5.2.1. Heel Stick

Equipment

a. heel warming device
b. alcohol wipes (Isopropyl alcohol 70% sterile)
c. pair of disposable gloves
d. Sterile lancet (Quikheel ™ or Tenderfoot ™ are commonly used)
e. 2x2 Gauze
f. Collection devices (Microtainers or 'bullets')
g. Bandage

Preparation

a. Approximately three minutes before you begin the heel stick process, apply the infant heel warming device to the infant's heel to increase the blood flow.
b. The site of the heel stick should be pink or normal color, and free of scars, cuts, bruises, or rashes. Do not choose a site that is cyanotic (bluish in color) or edematous (swollen).
c. Cleanse venipuncture site with an alcohol wipe, using circular motion toward the periphery. Allow area to dry before proceeding. This prevents the burning sensation for patients when venipuncture is performed and it prevents hemolysis of the blood.
d. Open the sterile lancet and remove from packaging right before puncture.

Heel Stick Procedure

a. Don gloves before grasping the foot in a firm, but gentle hold, by wrapping fingers around the bottom of the heel and around the top of the foot.
b. Position the lancet device on the site with firm, but gentle pressure, this assists in decreasing the sensation and ensures the puncture depth is adequate.
c. Puncture the heel on the sole of the foot with the Quickheel lancet device. Dispose of the device in a sharps box.
d. Apply gentle pressure to the site while wiping away the first drop of blood on a dry piece of gauze.
e. Position the infant's foot downward to enhance blood flow and continue to apply gentle pressure to the tissue surrounding the heel puncture site. It is important NOT to squeeze or massage too vigorously.
f. Collect the blood in appropriate microtainers by allowing droplets to naturally fall down the wall of the bullet. Scooping/scraping should be discouraged.
g. Tap the tube gently to encourage the settling of blood to the bottom of the tube. Cap and gently invert the bullets. Once collection is complete, apply pressure to the heel site with clean gauze until bleeding stops, then apply bandage.*
h. Dispose of contaminated materials in the sharps box, throw away opened materials not used, remove gloves, and wash hands.

***NOTE: If a cotton ball is used to help stop bleeding from a phlebotomy site, it should not be held in place by tape or a Band-Aid on a child less than 3 years old. Cotton balls should be held in place by an adult until bleeding from the site has stopped. Children less than 3 years old should not leave the office with a Band-Aid on the phlebotomy site unless it is requested by the parent and the risk of aspiration has been explained to the parent. An alternative to a Band-Aid is an adhesive wrap called Coban.**

13.5.2.2. Finger Stick

Capillary blood samples may be obtained when unable to get venous access, however, venous blood samples remain the priority.

In situations where a family cannot make a TEDDY visit either in a TEDDY Clinic or Long Distance Protocol, the family may be offered to do a home finger stick. This method should only be used when all other options have been exhausted. Detailed instruction via phone and written should be provided (see appendix for parent letter and home instruction sheet examples). Samples should be mailed overnight to the clinical center for processing.

NOTE: Home finger sticks should be reserved for subjects who have missed multiple TEDDY visits, not just for a subject missing one visit

(once a home capillary sample is offered it may be difficult to get the subject to come back to the clinic for an in-person visit).

NOTE: Since the capillary sample will be collected by a non-TEDDY staff member (parent/relative) the subject will be considered a Long-Distance Protocol subject and should be registered on the Long-Distance Protocol Registration Form.

NOTE: A "Gross Hemolysis" checkbox has been provided on the Serum SCFs for use for the capillary sample collections through either the standard protocol or the Long-Distance Protocol.

Home instructions and kits should include all of the components listed below for in clinic capillary sampling.

Equipment

a. warming device (washcloth, towel, diaper, or warming device)
b. alcohol wipes (Isopropyl alcohol 70% sterile)
c. pair of disposable plastic latex gloves
d. Sterile safety lancet or automated skin puncture device
e. 2x2 Gauze
f. Collection devices (Microtainers or 'bullets')
g. Bandage

Preparation

a. Warm the site for a minimum of 3 minutes to increase blood flow. To warm the site, use a washcloth, towel, or diaper that has been moistened with comfortable warm water (42 º C or 108 ºF) or a warming device can be applied to the site.
b. The site to be used for the finger stick should be warm, pink or normal color, and free of scars, cuts, bruises, or rashes. Do not choose a site that is cold, cyanotic (bluish in color), or edematous (swollen).
c. Cleanse venipuncture site with an alcohol wipe, using circular motion toward the periphery. Allow area to dry before proceeding. This prevents the burning sensation for patients when venipuncture is performed and it prevents hemolysis of the blood.
d. Open the sterile lancet and remove from packaging right before puncture.

Finger Stick Procedures

a. Grasp the finger between your thumb and index finger. Position the lancet device on the site with firm, but gentle pressure, this assists in decreasing the sensation and ensures the puncture depth is adequate.
b. Perform the puncture in the central, fleshy portion of the finger, slightly to the side of the center and perpendicular to the whorls (grooves) of the

fingerprint. It is important NOT to puncture the index finger or the little finger.

c. Apply gentle pressure to the site while wiping away the first drop of blood on a dry piece of gauze.
d. Position the site downward to enhance blood flow and continue to apply gentle intermittent pressure proximal to the site.
e. Collect the blood in appropriate microtainers by allowing droplets to naturally fall down the wall of the bullet. Scooping/scraping should be discouraged.
f. Tap the tube gently to encourage the settling of blood to the bottom of the tube. Cap and gently invert the bullets. Once collection is complete, apply pressure to the site with clean gauze until bleeding stops, then apply bandage.*
g. Dispose of contaminated materials in the sharps box, throw away opened materials not used, remove gloves, and wash hands.

***NOTE: If a cotton ball is used to help stop bleeding from a phlebotomy site, it should not be held in place by tape or a Band-Aid on a child less than 3 years old. Cotton balls should be held in place by an adult until bleeding from the site has stopped. Children less than 3 years old should not leave the office with a Band-Aid on the phlebotomy site unless it is requested by the parent and the risk of aspiration has been explained to the parent. An alternative to a Band-Aid is an adhesive wrap called Coban.**

Sample Priority for heelstick or fingerstick-based sampling

1. Begin sample collection in a microtainer with no additive for serum sample aliquoting; up to 200 µl of whole blood should be collected in the microtainer.
2. If good blood flow continues, collect in an EDTA (purple) microtainer, for HbA1c on autoantibody positive subjects.
3. Prioritizing the EDTA (purple) microtainer for HLA confirmation would only occur if this sample has not yet been obtained.

13.5.3. One-Time Blood Draw for Withdrawn Subjects

Aim: To increase options during the TEDDY Update Form contact to offer a low-burden method for obtaining primary endpoint data.

Method: Offering withdrawn subjects the option for a one-time blood sample collection via fingerstick or venipuncture for diabetes autoantibodies and the transglutaminase autoantibody
Eligibility: TEDDY subjects who are currently Inactive/Withdrawn who agree to have a one-time blood draw.

Payment: Site Specific

Human Subjects: Site Specific. Informed consent may need to be obtained from the withdrawn subjects using a one-time blood draw consent.

Data Management: Site should indicate if the subject accepted or refused the one-time blood draw or if it was not offered to the subject on the TEDDY Update Form. A Change in Study Participation will not be completed on the subjects who complete the one-time blood draw. If the subject selects to re-enroll in the follow-up, a Change in Study Participation will be completed (see MOO section 8.3.5.1. for instructions). This will change the subject's substatus from Withdrawn to Rejoined Study.

13.6. Random Blood Glucose (RBG)

Performance of Random Glucose Measurement:

Who: All personnel who will perform glucose measurement must be certified. At least one person at each Clinical Center must be certified.

Once an individual is certified at a clinical center, they can certify other personnel at their own site (but cannot certify personnel at another TEDDY site). It is recommended that at least one other person be certified in case of employee illness or staff turnover.

A random blood glucose measurement should be taken on all subjects at every clinic visit once they test positive for any autoantibody. This test can be done using a finger stick sample or a drop of blood from the venous sample taken at the clinic visit. Values equal or higher than 200 mg/dL (11.0 mmol/L) when confirmed in a local clinical laboratory are diagnostic for diabetes if the child has symptoms. If the child is asymptomatic, hyperglycemia must be confirmed on a subsequent day to meet diagnostic criteria (see recommendations below). If a venous blood glucose value cannot be obtained in a clinical laboratory, two finger prick blood glucoses will be taken. Values between 140-200 mg/dL (7.8-11.0 mmol/L) will trigger immediate assessment concerning signs and symptoms of diabetes and will be reported to a pediatric endocrinologist. Parents will be trained in home blood glucose monitoring with the recommendation to test RBG during child's illness and to check fasting and post-prandial glucose levels once every two weeks. Parents are instructed to call immediately if they measure two values ≥200 mg/dL (≥11.1 mmol/L) or one value ≥300 mg/dL (16.6 mmol/L) or at the first sign of diabetes symptoms. Written information about when to perform glucose checks and how to respond to values is preferred. Alternatively, an OGTT can be scheduled, or a new post-prandial glucose can be taken at the TEDDY clinic. While local arrangements may vary by center, the above instructions, follow-up and decision when to start insulin treatment will be supervised by a pediatric endocrinologist. However it is important to make sure that the ADA criteria for diagnosis are met before starting treatment.

NOTE: A clinical center can stop doing random blood glucose measurements on a subject who meets the following criteria:

1. There has been only 1 positive antibody sample in the child's life (excluding maternal transfer of autoantibodies)

AND

2. There have been 2 consecutive negative antibody samples after the positive

The type of glucometer used is site-specific. The manufacture meter instructions and calibration recommendations should be followed.

Log the blood glucose level on the subject's Physical Exam form for that particular visit. **Only random blood glucose measurements should be entered on the Physical Exam Form.**

The fasting blood glucose measurement from the OGTT is documented in the OGTT SCF.

13.7. OGTT

Who: All personnel who will perform OGTT must be certified. At least one person at each Clinical Center must be certified.

Requirement: OGTT Certification requires performance of an OGTT and proficiency reviewed by a certified person.

Procedures: Personnel seeking certification must observe an OGTT performed by a certified person. They then must correctly perform an OGTT either while being observed by a certified person or while being videotaped for review by a Study Coordinator. Videotaped procedures must be performed on a non-study subject, and proficient ability to perform the OGTT procedure must be demonstrated.

Once an individual is certified, they can certify other personnel at their own site (but cannot certify personnel at another TEDDY site). It is recommended that at least one other person be certified in case of employee illness or staff turnover.

An OGTT test will be performed every six months on every child who has tested positive for two or more autoantibodies (GADA, IAA, IA-2A, ZnT8A), regardless of autoantibody positivity confirmation or persistence, at any previous visit (but both antibodies must be positive at the same visit) and is three years of age or older. For children between the ages of 1 year and 3 years who have elevated random or fasting glucose levels, sites have the option of performing an OGTT on

the child. An OGTT performed on a child less than 3 years of age is completely optional and left to the discretion of the site.

Oral glucose is administered in a dose of 1.75 g/kg body weight to a maximum of 75 grams in children, as a solution in flavored water, consumed within 5 minutes. A six-time point OGTT is performed with venous samples at -10, 0, 30, 60, 90, 120 minutes, which includes sampling for glucose, insulin and C-peptide at all time-points. Glucose will be measured locally by meter at 0 minutes and 120 minutes. All samples will be shipped to the MMTT/OGTT laboratory for processing.

In March 2016, TEDDY recommendations shifted from a two-time point to a six-time point OGTT. A two-time point OGTT is an option and is still conducted at some centers.

A two-time point OGTT can still be performed if a child/family is not willing to have an IV placed or limits to staff availability. A two-time point OGTT is performed with venous blood for glucose determination collected before solution is ingested (called 0 minutes) (for rare cases when it is not possible to obtain a venous sample from the subject, a capillary glucose at 0 minutes is acceptable) and capillary glucose determined at 120 minutes (if venous blood is available at 120 minutes then venous blood should be used instead of capillary blood). Glucose will be measured locally by meter at 0 minutes and 120 minutes; the remaining blood from the 0 minute glucose sample should be shipped to the MMTT/OGTT lab for analysis and if a 120 minute venous glucose sample is available the remaining blood from this sample should also be shipped to the lab for analysis. Samples for insulin and C-peptide will be collected at time 0 minutes and 120 minutes (if venous blood is available) and shipped to the MMTT/OGTT lab for analysis. The lab has requested that sites place all of the subject's Insulin, Glucose and C-peptide samples collected at one visit right next to each other in the freezer box so that the samples can be analyzed together at the lab.

In rare situations when it is not possible to collect the 120 minute OGTT samples and the OGTT cannot be rescheduled, the 0 minute glucose, 0 minute c-peptide and 0 minute insulin samples should still be collected; the OGTT SCF should be completed following the instructions below:

<u>OGTT SCF:</u>

- Enter "0" for total dose of glucose if glucose was not drank by the subject
- Enter data related to 0 minute glucose, 0 minute c-peptide and 0 minute insulin samples only
- Do not enter blood glucose level for the 120 minute glucose sample, type of sample or # of minutes from time of blood draw to time of sample processing completion for any of the 120 minute samples

- Mark 'insufficient volume' for all other samples besides the 0 minute glucose, 0 minute c-peptide and 0 minute insulin samples

NOTE: The results of the OGTT will be used as part of the ADA criteria for diagnosing diabetes. If the 2-hour OGTT value (listed as #3 on the Diagnosis of Diabetes form) is the first criterion met for diabetes diagnosis the OGTT should be repeated within 60 days or confirmed by additional glucose values at home testing in accordance with instructions above. Parents may be asked to perform additional home BG testing to determine if there are values consistent with diabetes. However, confirmation of the diagnosis will always be made using glucose values reviewed or obtained by the TEDDY clinic

Abnormal OGTT

All study participants found to be positive for two or more islet autoantibodies will be asked to undergo standard OGTT every six months at the time of their regular TEDDY visit. Additionally, optional home blood glucose monitoring can be recommended to the families. Fasting BG>=126 mg/dL (7 mmol/L) or 2-hr BG >= 200 mg/dL (11.1 mmol/L) are diagnostic for diabetes and trigger immediate assessment concerning signs and symptoms of diabetes. A pediatric endocrinologist will be contacted. If the child has symptoms of diabetes and confirmed diabetic values as above, the diagnosis of diabetes will be made. While local arrangements may vary by center, the above instructions, follow-up and any decisions on when to start insulin treatment will be supervised by a pediatric endocrinologist.

If the child has no symptoms, the following alternative recommendations are made: Parents are advised to test fasting and post-prandial glucose for 3-7 days and report values back to the study staff. Families are instructed to call immediately if they measure two values ≥200 mg/dL (≥11.1 mmol/L) or one value ≥300 mg/dL (16.6 mmol/L) of at the first sign of diabetes symptoms. Written information about when to perform glucose checks and how to respond to values is preferred. Alternatively or additionally, a new OGTT can be scheduled within 60 days. Other methods of monitoring (ex: CGM) have been used at different clinical centers. While local arrangements may vary by center, the above instructions, follow-up and decision when to start insulin treatment will be supervised by a pediatric endocrinologist.

Impaired OGTT

Families of children with Impaired Glucose Tolerance (IGT) (2 hour glucose 140-200 mg/dL (7.8-11.0 mmol/L)) or Impaired Fasting Glucose (IFG) (FBG between 110-126 mg/dL (6.1-7.0 mmol/L)) on an OGTT will be given immediate instructions concerning signs and symptoms of diabetes. If not done previously, parents will be trained in home blood glucose monitoring with recommendation to test RBG during child's illness and fasting and post-prandial glucose based on TEDDY investigator/physician recommendations. Families are instructed to call immediately if they measure two values ≥200

mg/dL (≥11.1 mmol/L) or one value ≥300 mg/dL (16.6 mmol/L). Written information about when to perform glucose checks and how to respond to values is preferred. Alternatively or additionally, a new OGTT can be scheduled. While local arrangements may vary by center, the above instructions, follow-up and decision when to start insulin treatment will be supervised by a pediatric endocrinologist.

Home glucose monitoring is a site-specific practice. See Appendix M for details.

As much as possible this test should be scheduled before 10 am for the subject's comfort, as the subject must be fasting for at least 8 hours at the time of the test; the subject should not fast for longer than 16 hours though. The OGTT should be rescheduled if the subject has an acute illness.

Instructions for six-time point OGTT:

You will need the following supplies:

Calibrated Glucometer
EMLA Cream
I.V. Line
6 – 2 mL heparin tubes (green top)
6 – 2 mL potassium tubes (gray top)
6 – 2 mL EDTA tubes (purple top)
18 – 2 mL cryovials
Bucket of ice
Oral glucose solution (Glucola, Nutrical, GlucosePro, Accu-check), refrigerate until use
Collection tubes, cryovials, and venipuncture supplies used for venous sample collection and processing for the regular TEDDY clinic visit.

1. Confirm subject has only had water for the last 8 hours.

2. Obtain height and weight

3. Apply EMLA cream to antecubital sites as early as possible prior to venipuncture.

4. Prior to starting IV, test a finger poke sample by glucometer. If a value is > 126mg/dl (7 mmol/L) a pediatric endocrinologist should be consulted to proceed with the OGTT. This value is to confirm OGTT can be completed and is only recorded on the SCF if the OGTT is not performed.

5. Place an I.V. line into an optimal vein, using an intracatheter/butterfly needle (usually 22 or 24 gauge depending upon the size of the participant).

6. Before the procedure, fill several 3 mL syringes with luer-lock tips with 1 mL normal saline solution to flush the adapter after each blood draw. This is only necessary if the blood sampling is more than 3 minutes apart. Write specific time points with an alcohol-proof pen on each of the tubes.

7. Then complete blood draws for routine TEDDY visit. Test a drop of blood from this venipuncture by glucometer. Value should be < 126 mg/dL (or 7 mmol/L) in order to proceed with OGTT; if you proceed with OGTT record this value on the OGTT Sample Collection Form (SCF) in the corresponding field at the 0 minutes time point (see OGTT SCF instructions in section below). If the value is > 126 mg/dL (or 7 mmol/L) do not proceed with OGTT and refer subject for diabetic work-up.

8. Obtain samples, 1.0 ml should be collected for glucose in a potassium tube (gray top), 1.0 ml should be collected for c-peptide in an EDTA tube (purple top) and 1.0 ml should be collected for insulin in a heparin tube (green top) at each of the six time points:

    a. The first sample should be taken at least 10 minutes after establishing the line(s) and when participant is calm and relaxed (if possible, depending on age) - this is the "-10 minute" sample.
    b. The second sample should be taken just prior to drinking the Glucola - this is the "0 minute" sample.
    c. At time 0 minutes:

Administer Glucola calculated at 1.75 grams CHO per kg of body weight to a maximum of 75 grams. Subjects should be given a maximum of 5 minutes to completely drink the glucola.

Use Glucola 100g/300cc (1g= 3cc) **OR** 75g/300cc (1g= 4cc).
Be sure to note the dextrose amount listed on the Glucola bottle, 75g or 100g. It is strongly recommended that two staff members calculate the dosage amount in order to confirm that the calculation is correct.

- <u>For 100g/300cc</u>:
  1.75g x patient weight in kg x 3 = cc glucola
  Maximum dose 225cc or 75g

  <u>Example</u>: For 100g/300cc in a 15kg child:
  1.75g x 15kg x 3 = 78.75 cc glucola

- For 75g/300cc:
  1.75 x patient weight in kg x 4 = cc glucola
  Maximum dose 300cc or 75g

  Example: For 75g/300cc in a 15kg child:
  1.75 x 15kg x 4 = 105 cc glucola

If using Nutrical, refer to the table below:

TEDDY

Nutrical glucose tolerance test

Dosage and Instruction for use (Children)

For Children glucose bolus depend about child weight -> 1,75g/kg but not more than 75 g glucose.

1. Take Nutrical and water according to table.
2. Mix and wait a few minutes.

Weight kg	Nutrical ml	Water ml	Total volume ml	It is same than g glucose
10	26	43	69	17,3
11	29	48	77	19,2
12	32	53	85	21,2
13	34	56	90	22,6
14	37	61	98	24,6
15	40	66	106	26,6
16	42	70	112	27,9
17	45	74	119	29,9
18	47	78	125	31,2
19	50	83	133	33,2
20	53	88	141	35,2
21	55	91	146	36,5
22	58	96	154	38,5
23	61	101	162	40,5
24	63	104	167	41,8
25	66	109	175	43,8
26	69	114	183	45,8
27	71	118	189	47,1
28	74	122	196	49,1
29	76	126	202	50,4
30	79	130	209	52,4
31	82	135	217	54,4
32	84	139	223	55,8
33	87	144	231	57,7
34	90	149	239	59,7
35	92	152	244	61,1
36	95	157	252	63,1
37	98	162	260	65,0
38	100	166	266	66,4
39	103	170	273	68,4
40	105	174	279	69,7
41	108	179	287	71,7
42	111	183	294	73,7
43	113	187	300	75,0

The German TEDDY site has indicated that they are using Accu-Chek Dextrose O.G-T - The amount of glucose is the same as mentioned above for Glucola (75g Glucose and 300ml (=300cc) fluid). The calculation information is also according to the Glucola calculations, which is ***1.75g x Body weight in kg x 4 = ml Glucose solution***

The Tampere, Finland TEDDY site has indicated that they are using GlucosePro and Glucosol. The Oulu, Finland TEDDY site varies in which glucose solution is used, however the solution is administered in adherence to the TEDDY protocol and according to the concentration of the solution.

The Swedish site uses Nutrical. The site uses the table above.

GlucosePro instructions:
For children (weight less than 43 kg)

The amount of glucose must be 1.75 g per body weight (kilogram); max volume 250 ml.

To calculate the amount of solution:
The amount of GlucosePro solution (ml) = 3.33* the weight of a child (kg)* 1.75 g

Glucosol information: http://www.mistrymedical.com/item/13727/rapilose-glucose-tolerance-testing-solution-330ml--gtt-

d. Obtain post-Glucola blood samples: samples are taken at 30, 60, 90, and 120 minutes after time 0.

Sampling Protocol:

Time (minutes)	Glucose Sample Taken 2 mL potassium tube (gray top)	C-peptide Sample Taken 2 mL EDTA tube (purple top)	Insulin Sample Taken 2 mL heparin tube (green top)
-10	X	X	X
0	X	X	X
Drink Glucola			
30	X	X	X
60	X	X	X
90	X	X	X
120	X	X	X

e. Immediately invert each tube gently 8-10 times to mix sample, avoid jarring or shaking, then place upright on ice or in refrigerator; spin samples at approximately 1200 to 1300 x g for 10 minutes in a chilled centrifuge within 1 hour after drawing and aliquot as listed below:
   i. transfer C-peptide plasma sample into a purple top cryovial
   ii. transfer Insulin plasma sample into green top cryovial
   iii. transfer Glucose plasma sample into a gray top cryovial
   iv. Refrigerate samples after aliquoting into cryovials until freezing. Store samples at -70°C as soon as possible. The lab has requested that sites place all of the subject's Glucose and C-peptide samples collected at one visit right next to each other in the freezer box so that the samples can be analyzed together at the lab.

9. At 120 minutes test a drop of blood from this venipuncture by glucometer. Record this value on the OGTT Sample Collection Form (SCF) in the corresponding field at the 120 minutes time point (see OGTT SCF instructions in section below).

10. Termination of OGTT: test is terminated after the blood sample at 120 minutes is obtained. At that time, the indwelling cannula(e) will be withdrawn, pressure applied and a sterile strip bandage applied.

11. Upon completion of the test, bandage the blood draw site and the participant should have a snack, for example peanut butter or cheese crackers, coffee, milk or ginger ale (be sure to have gluten-free snacks available).

12. The samples should be shipped to the MMTT/OGTT lab for analysis. The lab has requested that sites place all of the subject's Insulin, Glucose and C-peptide samples collected at one visit right next to each other in the freezer box so that the samples can be analyzed together at the lab.

Instructions for two-time point OGTT (for children who are not willing to participate in a six-time point OGTT):

You will need the following supplies:

Calibrated Glucometer
EMLA Cream
1 – 2 mL heparin tube (green top) (2 – 2 mL heparin tubes will be needed if venous blood is available at 120 minutes)
1 – 2 mL potassium tube (gray top) (2 – 2 mL potassium tubes will be needed if venous blood is available at 120 minutes)
1 – 2 mL EDTA tube (purple top) (2 – 2 mL EDTA tubes will be needed if venous blood is available at 120 minutes)
3 – 2 mL cryovials (6 – 2 mL cryovials will be needed if venous blood is available at 120 minutes)
Bucket of ice
Glucola oral glucose solution, refrigerate until use
Collection tubes, cryovials, and venipuncture supplies used for venous sample collection and processing for the regular TEDDY clinic visit.

1. Confirm subject has only had water for the last 8 hours.

2. Obtain height and weight

3. Apply EMLA cream to antecubital sites as early as possible prior to venipuncture. Then perform venipuncture for routine TEDDY visit and baseline OGTT:
   - Draw appropriate volume for TEDDY visit labs, plus:

- Draw 1ml of blood into a heparin tube (green top) for insulin
- Draw 1ml of blood into a potassium tube (gray top) for glucose
- Draw 1ml of blood into an EDTA tube (purple top) for C-peptide

4. Blood tubes should be placed on ice after drawing.

5. Test a drop of blood from this venipuncture by glucometer. Value should be < 126 mg/dL (or 7 mmol/L) in order to proceed with OGTT; if you proceed with OGTT record this value on the OGTT Sample Collection Form (SCF) in the corresponding field at the 0 minutes time point (see OGTT SCF instructions in section below). If the value is > 126 mg/dL (or 7 mmol/L) do not proceed with OGTT and refer subject for diabetic work-up.

6. At time 0 minutes:

Administer Glucola calculated at 1.75 grams CHO per kg of body weight to a maximum of 75 grams. Subjects should be given a maximum of 5 minutes to completely drink the glucola.

Use Glucola 100g/300cc (1g= 3cc) **OR** 75g/300cc (1g= 4cc).
Be sure to note the dextrose amount listed on the Glucola bottle, 75g or 100g. It is strongly recommended that two staff members calculate the dosage amount in order to confirm that the calculation is correct.

- For 100g/300cc:
  1.75g x patient weight in kg x 3 = cc glucola
  Maximum dose 225cc or 75g

  Example: For 100g/300cc in a 15kg child:
  1.75g x 15kg x 3 = 78.75 cc glucola

- For 75g/300cc:
  1.75 x patient weight in kg x 4 = cc glucola
  Maximum dose 300cc or 75g

  Example: For 75g/300cc in a 15kg child:
  1.75 x 15kg x 4 = 105 cc glucola

If using Nutrical, refer to the table below:

Nutrical glucose tolerance test

Dosage and Instruction for use (Children)

For Children glucose bolus depend about child weight -> 1,75g/kg but not more than 75 g glucose.

1. Take Nutrical and water according to table.
2. Mix and wait a few minutes.

Weight kg	Nutrical ml	Water ml	Total volume ml	It is same than g glucose
10	26	43	69	17,3
11	29	48	77	19,2
12	32	53	85	21,2
13	34	56	90	22,6
14	37	61	98	24,6
15	40	66	106	26,6
16	42	70	112	27,9
17	45	74	119	29,9
18	47	78	125	31,2
19	50	83	133	33,2
20	53	88	141	35,2
21	55	91	146	36,5
22	58	96	154	38,5
23	61	101	162	40,5
24	63	104	167	41,8
25	66	109	175	43,8
26	69	114	183	45,8
27	71	118	189	47,1
28	74	122	196	49,1
29	76	126	202	50,4
30	79	130	209	52,4
31	82	135	217	54,4
32	84	139	223	55,8
33	87	144	231	57,7
34	90	149	239	59,7
35	92	152	244	61,1
36	95	157	252	63,1
37	98	162	260	65,0
38	100	166	266	66,4
39	103	170	273	68,4
40	105	174	279	69,7
41	108	179	287	71,7
42	111	183	294	73,7
43	113	187	300	75,0

The German TEDDY site has indicated that they are using Accu-Chek Dextrose O.G-T - The amount of glucose is the same as mentioned above for Glucola (75g Glucose and 300ml (=300cc) fluid). The calculation information is also according to the Glucola calculations, which is ***1.75g x Body weight in kg x 4 = ml Glucose solution***

The Tampere, Finland TEDDY site has indicated that they are using GlucosePro and Glucosol. The Oulu, Finland TEDDY site varies in which glucose solution is used, however the solution is administered in adherence to the TEDDY protocol and according to the concentration of the solution.

GlucosePro instructions:
For children (weight less than 43 kg)

The amount of glucose must be 1.75 g per body weight (kilogram); max volume 250 ml.

To calculate the amount of solution:
The amount of GlucosePro solution (ml) = 3.33* the weight of a child (kg)* 1.75 g

Glucosol information: http://www.mistrymedical.com/item/13727/rapilose-glucose-tolerance-testing-solution-330ml--gtt-

7. Spin baseline samples at approximately 1200 to 1300 x g for 10 minutes and aliquot as listed below:
   - transfer C-peptide plasma sample into a purple top cryovial
   - transfer Insulin plasma sample into green top cryovial
   - transfer Glucose plasma sample into a gray top cryovial
   - Refrigerate samples after aliquoting into cryovials until freezing. Store samples at -70°C as soon as possible.

8. At time 60 minutes, apply EMLA cream to finger site of future fingerstick, or to antecubital site of future venous draw and cover with bandage.

9. At time 120 minutes, remove bandage, wipe finger with alcohol swab, let airdry, and use springloaded lancet to test one drop of fingerstick capillary blood by glucometer and record this value on OGTT SCF in corresponding field at the 120 minutes time point (see OGTT SCF instructions in section below). If venous blood is available at 120 minutes then venous blood should be used instead of capillary blood for the insulin, glucose and c-peptide samples and the collection and processing instructions listed for the 0 minutes insulin, glucose and c-peptide samples should be followed.

10. Bandage the blood draw sites and give the subject a meal.

11. The remaining blood from the 0 minute glucose sample should be shipped to the MMTT/OGTT lab for analysis and if a 120 minute venous glucose sample is available the remaining blood from this sample should also be shipped to the lab for analysis. The insulin and C-peptide samples collected at time 0 minutes and 120 minutes (if venous blood is available) should be shipped to the MMTT/OGTT lab for analysis. The lab has requested that sites place all of the subject's Insulin, Glucose and C-peptide samples collected at one visit right next to each other in the freezer box so that the samples can be analyzed together at the lab.

OGTT Sample Collection Form

The SCFs contain constraints that prevent a vial barcode number from being saved more than once. If you try to save a vial barcode number that has already been saved, an error message will appear that explains why the new information cannot be saved. If the vial barcode number that you are trying to save is correct and the same vial barcode number has been entered (and saved) incorrectly for a subject that is within your clinical center, please try to determine the mistake that was made and correct appropriately on the TEDDY website (the Local Code, Subject ID, Visit

Name and Test Name associated with the other sample will be provided in the error message) – if you are unable to make the correction yourself contact the DCC at **TEDDY@epi.usf.edu** to make the correction for you. If the sample has already been sent to the Repository or Lab, please contact the Repository or Lab and the DCC with the correct information; once the Repository or Lab verifies that the new information you have given is correct then you should correct this information on the TEDDY website – if you are unable to make the correction yourself contact the DCC at **TEDDY@epi.usf.edu** to make the correction for you. If the vial barcode number was incorrectly entered and saved for a subject that is not within your clinical center, please contact the DCC at **TEDDY@epi.usf.edu**

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject
4. Under "Search Results", click on the Local Code of the desired subject.
5. For subjects who meet the following requirements the OGTT SCF will display in the Participant's Details Page schedule: An OGTT test will be performed every six months on every child who has tested positive for two or more autoantibodies, regardless of autoantibody positivity confirmation or persistence, at any previous visit (but both antibodies must be positive at the same visit) and is three years of age or older.
6. For children between the ages of 1 year and 3 years who have elevated random or fasting glucose levels, sites have the option of performing an OGTT on the child. An OGTT performed on a child less than 3 years of age is completely optional and left to the discretion of the site. For these subjects the site should choose "OGTT Sample Collection Form" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
7. Click 'Select Form' button that is below dropdown menu.
8. Subject ID, Local Code, and Clinical Center fields will be prepopulated on the Sample Collection Form
9. Choose the visit location code from the drop down menu and enter the Date of Draw (DD/MMM/YYYY) on this form.
10. **If the blood sample was processed according to standard TEDDY protocol** (i.e. the Long-Distance protocol was not followed):
    a. Mark the "Sample processed according to standard protocol or Standard protocol followed, insufficient volume" checkbox (note: you should also mark this box when there is an insufficient volume of blood for all of the OGTT lab samples, but blood glucose levels were still able to be obtained at the TEDDY visit during the OGTT) and continue to step 11.

If the OGTT was administered via the Long-Distance protocol:

a. And there was an insufficient blood volume for all of the OGTT lab samples, but blood glucose levels were still able to be obtained, mark the "Long Distance Protocol Insufficient Volume" checkbox and continue to step 11 **OR**
b. If there was a sufficient amount of blood for at least one of the OGTT lab samples on the SCF indicate the date and time that the sample was processed (this is the time the sample was put in the freezer) and continue to step 11 (remote lab that actually collected the sample should indicate the date the sample was drawn, time the sample was drawn and date the sample was shipped in Section 3c of the corresponding Physical Exam Form).

NOTE: If sample was drawn/collected in a Long-Distance protocol lab that is in a different time zone than the TEDDY Clinical Center the time the sample was drawn and the time the sample was processed should be indicated in the time zone of the Clinical Center and this should be noted on the Physical Exam Form source document received from the Long-Distance protocol lab

11. Enter the total dose of glucose in grams in the corresponding field.
12. For the -10 minutes Insulin sample, indicate the type of sample (venous blood or venous plasma) and enter the time the sample was drawn and the time the sample was processed (the time sample is placed in freezer). If the subject refused the six time-point OGTT and a two time-point OGTT was completed instead, leave these data fields blank.
13. For the -10 minutes Glucose sample, indicate the type of sample (venous blood or venous plasma) and enter the time the sample was drawn and the time the sample was processed (the time sample is placed in freezer). If the subject refused the six time-point OGTT and a two time-point OGTT was completed instead, leave these data fields blank.
14. For the -10 minutes C-peptide sample, indicate the type of sample (venous blood or venous plasma) and enter the time the sample was drawn and the time the sample was processed (the time sample is placed in freezer). If the subject refused the six time-point OGTT and a two time-point OGTT was completed instead, leave these data fields blank.
15. For the 0 minutes Insulin sample, indicate the type of sample (venous blood or venous plasma) and enter the time the sample was drawn and the time the sample was processed (the time sample is placed in freezer).
16. For the 0 minutes Glucose sample, enter the blood glucose level (in mg/dL or mmol/L; note the Swedish sites should enter a blood glucose

level in both the Hemocue1 field and Hemocue2 field), indicate the type of sample (venous blood, capillary blood or venous plasma) and enter the time the sample was drawn and the time the sample was processed (the time sample is placed in freezer).

17. For the 0 minutes C-peptide sample, indicate the type of sample (venous blood or venous plasma) and enter the time the sample was drawn and the time the sample was processed (the time sample is placed in freezer).
18. For the 30 minutes Insulin sample, indicate the type of sample (venous blood or venous plasma) and enter the time the sample was drawn and the time the sample was processed (the time sample is placed in freezer). If the subject refused the six time-point OGTT and a two time-point OGTT was completed instead, leave these data fields blank.
19. For the 30 minutes Glucose sample, indicate the type of sample (venous blood or venous plasma) and enter the time the sample was drawn and the time the sample was processed (the time sample is placed in freezer). If the subject refused the six time-point OGTT and a two time-point OGTT was completed instead, leave these data fields blank.
20. For the 30 minutes C-peptide sample, indicate the type of sample (venous blood or venous plasma) and enter the time the sample was drawn and the time the sample was processed (the time sample is placed in freezer). If the subject refused the six time-point OGTT and a two time-point OGTT was completed instead, leave these data fields blank.
21. For the 60 minutes Insulin sample, indicate the type of sample (venous blood or venous plasma) and enter the time the sample was drawn and the time the sample was processed (the time sample is placed in freezer). If the subject refused the six time-point OGTT and a two time-point OGTT was completed instead, leave these data fields blank.
22. For the 60 minutes Glucose sample, indicate the type of sample (venous blood or venous plasma) and enter the time the sample was drawn and the time the sample was processed (the time sample is placed in freezer). If the subject refused the six time-point OGTT and a two time-point OGTT was completed instead, leave these data fields blank.
23. For the 60 minutes C-peptide sample, indicate the type of sample (venous blood or venous plasma) and enter the time the sample was drawn and the time the sample was processed (the time sample is placed in freezer). If the subject refused the six time-point OGTT and a two time-point OGTT was completed instead, leave these data fields blank.
24. For the 90 minutes Insulin sample, indicate the type of sample (venous blood or venous plasma) and enter the time the sample was drawn and the time the sample was processed (the time sample is placed in

freezer). If the subject refused the six time-point OGTT and a two time-point OGTT was completed instead, leave these data fields blank.

25. For the 90 minutes Glucose sample, indicate the type of sample (venous blood or venous plasma) and enter the time the sample was drawn and the time the sample was processed (the time sample is placed in freezer). If the subject refused the six time-point OGTT and a two time-point OGTT was completed instead, leave these data fields blank.
26. For the 90 minutes C-peptide sample, indicate the type of sample (venous blood or venous plasma) and enter the time the sample was drawn and the time the sample was processed (the time sample is placed in freezer). If the subject refused the six time-point OGTT and a two time-point OGTT was completed instead, leave these data fields blank.
27. For the 120 minutes Insulin sample, indicate the type of sample (venous blood or venous plasma) and enter the time the sample was drawn and the time the sample was processed (the time sample is placed in freezer).
28. For the 120 minutes Glucose sample, enter the blood glucose level (in mg/dL or mmol/L note the Swedish sites should enter a blood glucose level in both the Hemocue1 field and Hemocue2 field), indicate the type of sample (venous blood, capillary blood or venous plasma) and enter the time the sample was drawn and the time the sample was processed (the time sample is placed in freezer).
29. For the 120 minutes C-peptide sample, indicate the type of sample (venous blood or venous plasma) and enter the time the sample was drawn and the time the sample was processed (the time sample is placed in freezer).
30. Find the row containing the “Test Name” (i.e. -10 minutes Insulin, -10 minutes Glucose, -10 minutes C-peptide, 0 minutes Insulin, 0 minutes Glucose, 0 minutes C-peptide, etc) of the sample in the vial you would like to scan. If an insufficient blood volume amount was obtained, and there is not enough blood for that particular Test Name or if the subject refused the six time-point OGTT and a two time-point OGTT was completed instead, check the “Insufficient Blood Volume” Box in that row, repeat this step as necessary then continue to step 37; if there is a sufficient amount of blood go to step 31.
31. Place cursor in the “Vial Barcode Number” box in this row.
32. Scan the preprinted barcode located on the cryovial containing this particular sample.
33. In the provided space, enter the sample volume (mL) contained in the cryovial.
34. In the provided space enter box number and space number where the sample will be stored.
35. Place the cryovial in the exact freezer box and space number that you entered on the SCF for that particular sample. The lab has requested

that sites place all of the subject's Insulin, Glucose and C-peptide samples collected at one visit right next to each other in the freezer box so that the samples can be analyzed together at the lab.

36. Repeat steps 30-35 as necessary.
37. When all information for this specific SCF has been entered, click the "Save Form" button at the top of this form.
38. Store the samples at -70°C. If a six time-point OGTT was completed the Insulin, Glucose and C-peptide samples from all six time-points should be shipped to the MMTT/OGTT lab for analysis. If a two time-point OGTT was completed the remaining blood from the 0 minute glucose sample should be shipped to the MMTT/OGTT lab for analysis and if a 120 minute venous glucose sample is available the remaining blood from this sample should also be shipped to the lab for analysis; the insulin and C-peptide samples collected at time 0 minutes and 120 minutes (if venous blood is available) should be shipped to the MMTT/OGTT lab for analysis. The lab has requested that sites place all of the subject's Insulin, Glucose and C-peptide samples collected at one visit right next to each other in the freezer box so that the samples can be analyzed together at the lab. Send samples to the lab in bulk shipments on dry ice once a month.

For the forms chosen from the "Additional Study Forms" dropdown menu, once the Participant's Details Page has been refreshed, you will see "OGTT Sample Collection Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1. Click on the form link under 'Completed Additional Study Forms'
2. A new window will open which will have a link to the "OGTT Sample Collection Form(s)" that has been saved for this subject.
3. Click on the 'View/Edit/Print" link to open up the specific form for this subject.

Shipping OGTT Samples

Entering information into the "Sample Shipment System"

1. Go to the "Sample Shipment System" located on the left navigational toolbar under "Data Management".
2. Enter the date of shipment.
3. If you have user access to more than one shipment origin, you will need to choose which destination the samples you are shipping are being shipped from. If you only have user access to one shipment origin, the 'Origin' drop-down menu will be defaulted to that location and you do not need to do anything.
4. Choose the "OGTT Lab (UF)" destination option under "Select where samples will be shipped to".

5. Enter the freezer box number(s) (numbers separated by commas) that you are going to be shipping that day and click "Search".
6. The Local Code, Subject ID, Clinical Center, Test Name, Vial Barcode Number, Visit Location Code, Box/Pouch Number, Space Number, Sample Volume and "Delete From Shipment" option will appear for all the samples that are located in the box(es).
7. Enter the tracking number and courier service for that shipment.
8. Click on "Print and Email Shipping List". A dialog box will open that asks "Are you sure you want to print and email the shipment list?" Press 'OK' if you do and 'Cancel' if you don't.
9. Once 'OK' has been clicked an Excel file will be created that will contain information pertaining to each sample (Vial Barcode Number, Subject ID, etc).
10. Save this file for your records; an email containing this file will automatically be sent to the DCC and to the MMTT/OGTT Lab.
11. Print out a copy of this list to be shipped with the samples.
12. Repeat this process as necessary until all the boxes you will be sending that day have been entered.

Packing and Shipping Instructions:

1. Please do not ship packages on Friday. The MMTT/OGTT lab is closed for business on weekends.
2. Place the freezer box along with a STP-152 absorbent strip inside a STP-731 inner leak proof poly (plastic) bag. Seal the bag.

   NOTE: Since TEDDY is using the same lab for OGTT and Thyroid antibody analyses, OGTT samples and Thyroid samples can be shipped together to the lab (in different freezer boxes). Please make sure that each freezer box is labeled either "OGTT" or "Thyroid".
3. Place the poly bag inside a STP-730 envelope, fold over and tuck the STP-730 into pocket.
4. Place the STP-730 envelope in the center of the STP-309 shipper.
5. Fill the remainder of the space between the STP-730 envelope and the inner walls of the cooler with dry ice.
6. Put the lid on the cooler and place the excel printout (containing the sample information) on top of the cooler. Place the "empty packaging cover" (if included – this will be one piece of cardboard that is attached to the outside of the box) on top of the list.
7. Close and tape the outer cardboard box.
8. Attach labels to side of box with "Biological Products Diagnostic Specimens" statement:
   a. Stick the dry ice label in the upper left corner. Enter the weight of dry ice in kg on the label.
   b. Stick a separate address label in the lower left corner under the dry ice label.
   c. Don't cover the words "Diagnostic Specimens"

9. **For shipments within the United States** use the pre-printed FedEx US air bill provided to you to ship the specimens to the MMTT/OGTT Lab.

a. In Section 1, enter the date, your name and phone number. (Sender's FedEx Account Number, Company and Address information should be already pre-printed on the air bill).
b. Section 3, should already be pre-printed on the air bill with MMTT/OGTT Lab address

UFHPL Endocrine Lab
ATTN: Dave Pittman
4800 SW 35 Drive
Gainesville, FL 32608
(352) 265-9900
UF_TEDDY@Pathology.ufl.edu

c. Under Section 4a, Express Package Service, mark "FedEx Standard Overnight".
d. Complete Section 5, Packaging
e. Complete Section 6, Special Handling:
    i. Under "Does this shipment contain dangerous goods?" check "Yes, Shippers Declaration not required".
    ii. Check the "Dry Ice" block and enter "1" x "#" kg. This is the total weight of dry ice added to the shipping box, in kg.
f. Under Section 7, Payment:
    i."Sender" should be pre-marked (DCC account information is listed on the Sender section)
    ii.Enter "1" under "Total Packages".
    iii.Weigh the package and indicate the weight of the package under "Total Weight"
g. Follow the peel and stick instructions on the back of the air bill (no document holder required).
h. Attach the air bill to the lower right corner of the side of the box.
i. Call FedEx at 1.800.Go.FedEx® (800.463.3339) or go to http://www.fedex.com/us/ to schedule a pick-up
j. Attach "Biological Substance Category B" label to one side of shipping box.
k. Fill out "Dry Ice" label and attach to one side of shipping box – include dry ice weight (kg), ship to and ship from information.

10. **For shipments within Europe** use the preprinted World House Air Way Bill (HAWB) to ship the samples to the MMTT/OGTT Lab. **PLEASE DO NOT SEND SHIPMENTS ON THURSDAY OR FRIDAY IN ORDER TO AVOID THAWING OF SAMPLES OVER THE WEEKEND.**
    a. Complete the sections of the HAWB that have not been pre-printed
    b. Affix the HAWB to the exterior of the shipper. This form is an internal tracking form used by World to identify your shipment from pick-up to delivery. When inquiring about your shipment, reference the waybill number

in the top right hand corner. World Courier will provide these forms to you with shipper and consignee information pre-printed.

c. World will send you an example Customs Invoice, you need to copy this invoice to your letterhead, fill in information for the Date, Shipper, Consignee, and estimate the amount of sample contained in the shipment (in mL) and sign.
d. Affix the Customs Invoice to the shipper exterior.
e. Along with the documents listed above, also give the signed Declaration Statement to the World Courier person picking up the shipment.
f. Call World Courier Services to arrange for pick-up:
    - Finland: 9 8700 3300
    - Sweden: 8 59441 480
g. You will need to provide the following information to the World Courier Representative:
    - DCC Account Number: 10848
    - Time of Pick-up
    - Specification of types of samples being sent
    - Number and type of boxes being shipped
    - Special Instructions: Diagnostic shipment

13.8. Optional Mixed Meal Tolerance Test (MMTT)

An optional Mixed Meal Tolerance Test (MMTT) will be added to the TEDDY Post-Diagnosis visit to measure c-peptide and glucose levels at 7 time-points. The oral mixed meal formula (Boost®, Mead Johnson Nutritional Division, Evansville, Indiana) is administered in a dose of 6 mL/kg, up to 360 mL. Glucose will be measured locally. C-peptide samples and the remainder of the glucose samples will be shipped to the MMTT/OGTT Reference Lab for measurement. The lab has requested that sites place all of the subject's Glucose and C-peptide samples collected at one visit right next to each other in the freezer box so that the samples can be analyzed together at the lab.

Who: All personnel who will perform MMTT must be certified. At least one person at each Clinical Center must be certified.

Requirement: MMTT Certification requires performance of a MMTT and proficiency reviewed by a certified person.

Procedures: Personnel seeking certification must observe a MMTT performed by a certified person. They then must correctly perform a MMTT either while being observed by a certified person or while being videotaped for review by a Study Coordinator. Videotaped procedures must be performed on a non-study subject, and proficient ability to perform the MMTT procedure must be demonstrated.

Once an individual is certified, they can certify other personnel at their own site (but cannot certify personnel at another site). It is recommended that at least one other person be certified in case of employee illness or staff turnover.

Mixed Meal Dose: The test meal (Boost) is given at a dose of 6 mL per kilogram body weight. Maximum dose is 360 mL. Boost is supplied in 8 fluid ounce cans.

NOTE: Should a subject have a milk allergy and not be able to drink the Boost product, it has been approved that the Kate Farms product listed below could be given to the subject for the study MMTT instead of the Boost product.

NOTE: In rare situations should a subject not want to drink the Boost High Protein Meal a checkbox is available on the MMTT SCF for "Boost High Protein Meal not given to subject, but samples still collected".

High Protein Boost

Nutrition Facts
Serving Size 1 bottle (237mL)

Amount Per Serving	
Calories 240	Calories from Fat 50
	% Daily Value*
Total Fat 6g	**9%**
Saturated Fat 1g	**5%**
Trans Fat 0g	
Cholesterol 10mg	**3%**
Sodium 200mg	**8%**
Potassium 450mg	**13%**
Total Carbohydrate 33g	**11%**
Dietary Fiber 0g	**0%**
Sugars 27g	
Protein 15g	**30%**

Vitamin A (50% as beta-carotene)			25%
Vitamin C	100%	• Calcium	35%
Iron	25%	• Vitamin D	60%
Vitamin E	100%	• Vitamin K	40%
Thiamin	25%	• Riboflavin	25%
Niacin	20%	• Vitamin B_6	35%
Folic Acid	25%	• Vitamin B_{12}	35%
Biotin	25%	• Pantothenic Acid	25%
Phosphorus	30%	• Iodine	25%
Magnesium	25%	• Zinc	30%
Selenium	25%	• Copper	25%
Manganese	35%	• Chromium	25%
Molybdenum	25%	• Chloride	8%

*Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

	Calories:	2,000	2,500
Total Fat	Less than	65g	80g
Sat Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Potassium		3,500mg	3,500mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g
Protein		50g	65g

Contains 55mg choline per serving, which is 10% of the Daily Value (DV) for choline (550mg).

INGREDIENTS: WATER, SUGAR, MILK PROTEIN CONCENTRATE, CORN SYRUP, VEGETABLE OIL (CANOLA, HIGH OLEIC SUNFLOWER, CORN), COCOA PROCESSED WITH ALKALI, SOY PROTEIN ISOLATE, CALCIUM CASEINATE, SODIUM CASEINATE, AND LESS THAN 0.5% OF POTASSIUM CITRATE, MAGNESIUM CHLORIDE, CALCIUM PHOSPHATE, SALT, MAGNESIUM PHOSPHATE, CELLULOSE GEL AND GUM, SOY LECITHIN, SODIUM ASCORBATE, CHOLINE BITARTRATE, ALPHA-TOCOPHERYL ACETATE, ASCORBIC ACID, CARRAGEENAN, POTASSIUM CHLORIDE, FERRIC PYROPHOSPHATE, NATURAL AND ARTIFICIAL FLAVOR, ZINC SULFATE, VITAMIN A PALMITATE, NIACINAMIDE, VITAMIN D_3, CALCIUM PANTOTHENATE, MANGANESE SULFATE, COPPER SULFATE, PYRIDOXINE HYDROCHLORIDE, THIAMINE HYDROCHLORIDE, BETA-CAROTENE, RIBOFLAVIN, CHROMIUM CHLORIDE, FOLIC ACID, BIOTIN, POTASSIUM IODIDE, PHYTONADIONE, SODIUM SELENITE, SODIUM MOLYBDATE, VITAMIN B_{12}.

CONTAINS: MILK AND SOY INGREDIENTS

Kate Farms, Vanilla Bliss

NUTRITION FACTS
Serving Size 1 Carton (330ml)

Amount/Serving	
Calories 310	Calories from Fat 80
	% Daily Value*
Total Fat 8g	12%
Saturated Fat 1g	5%
Trans Fat 0g	
Cholesterol 0mg	0%
Sodium 125mg	5%
Potassium 80mg	2%
Total Carbohydrate 44g	15%
Dietary Fiber 5g	20%
Sugars 19g	
Protein 17g	

Vitamin A 35%	Vitamin C 35%
Calcium 35%	Iron 15%
Vitamin D 35%	Vitamin E 35%
Thiamine 35%	Riboflavin 35%
Niacin 35%	Vitamin B6 35%
Folate 35%	Vitamin B12 35%
Biotin 35%	Pantothenic Acid 35%
Phosphorus 35%	Iodine 35%
Magnesium 35%	Zinc 35%
Selenium 35%	Copper 35%
Manganese 35%	Chromium 35%
Molybdenum 35%	

*Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

	Calories:	2,000	2,500
Total Fat	Less than	65g	80g
Sat Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g

Calories per gram:
Fat 9 • Carbohydrate 4 • Protein 4

Kate Farms, Cocoa Fudge

NUTRITION FACTS
Serving Size 1 Carton (330ml)

Amount/Serving	
Calories 330	Calories from Fat 80
	% Daily Value*
Total Fat 9g	14%
Saturated Fat 1g	5%
Trans Fat 0g	
Cholesterol 0mg	0%
Sodium 95mg	8%
Potassium 370mg	10%
Total Carbohydrate 45g	15%
Dietary Fiber 5g	20%
Sugars 19g	
Protein 19g	

Vitamin A 35%	Vitamin C 35%
Calcium 35%	Iron 15%
Vitamin D 35%	Vitamin E 35%
Thiamine 35%	Riboflavin 35%
Niacin 35%	Vitamin B6 35%
Folate 35%	Vitamin B12 35%
Biotin 35%	Pantothenic Acid 35%
Phosphorus 35%	Iodine 35%
Magnesium 35%	Zinc 35%
Selenium 35%	Copper 35%
Manganese 35%	Chromium 35%
Molybdenum 35%	

*Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

	Calories:	2,000	2,500
Total Fat	Less than	65g	80g
Sat Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g

Calories per gram:
Fat 9 • Carbohydrate 4 • Protein 4

The MMTT takes approximately two hours to complete, and must be scheduled in the morning (i.e. must be started before 10 AM). It is important to carefully review the eligibility criteria with the participant before starting the test, since if certain criteria have been violated the test will need to be rescheduled for another date. The MMTT should be rescheduled if the subject has an acute illness.

You will need the following supplies:

EMLA Cream
7 x 1.2 mL lavender top EDTA collection tubes (C-Peptide)
7 x 1.2 mL gray top Oxalate/Fluoride collection tubes (Glucose)
14 – 2 mL etched cryovials
Bucket of ice
Boost®, Mead Johnson Nutritional Division

Procedure:

1. The MMTT must begin between 7:00 - 10:00 a.m. for proper interpretation.

2. Ensure the subject is currently fasting (for at least 8 hours, but not longer than 16 hours) and complete the MMTT Procedure Form.

   NOTE: If the blood glucose fingerstick reading prior to the -10 minute timepoint is <60 mg/dL or >250 mg/dL or <3.3 mmol/L or >13.9 mmol/L the MMTT should be rescheduled.

   In rare situations when it is not possible to reschedule the MMTT, the -10 minute timepoint glucose and c-peptide samples should be collected and the MMTT Procedure Form and MMTT SCF should be completed following the instructions below:

   MMTT Procedure Form:
   - In these situations site should only complete questions #1-6 and times for -10 minute glucose and -10 minute c-peptide samples

   MMTT SCF:
   - Enter data related to -10 minute glucose and -10 minute c-peptide samples only
   - Do not enter type of sample or time sample was processed for any of the other samples
   - Mark 'insufficient volume' for all other samples besides -10 minute glucose and -10 minute c-peptide samples

3. Obtain the weight of the participant and calculate Boost meal size = 6 mL/kg, up to 360 mL (1 lb = 0.45 kg)
   a. The MMTT test uses a standard oral mixed meal formula (Boost®, Mead Johnson Nutritional Division, Evansville, Indiana) composed of liquid sucrose, soy protein, casein, and soy oil.
   b. Dosing: Below is a dosing calculation for the amount of Boost to be given to the participant:

DOSE CALCULATION WORKSHEET	
BOOST Dose: • 6 mL/kg up to a maximum of 360 mL. BOOST cans contain 8 fluid-ounces (240 mL) **BOOST Dose Calculation** Subject's weight in pounds_____ multiply by 0.454 = _____kg Subject's weight in kg _____ multiply by 6 = _____ mL of BOOST (not to exceed 360 mL) **Example:** a person weighing 110 pounds weighs 110 lbs x 0.454 = 49.9 kg and requires a dose of BOOST 49.9 kg x 6 = 299.4 mL (about one and one-fourth cans)	BOOST Dose Given: _____**mLs** (BOOST dose in m

4. The participant should remain sitting or resting in bed quietly throughout the test. *Note: The participant can engage in quiet, non-strenuous activities such as reading, playing cards, watching TV and may walk to the bathroom between blood draws if necessary (but should otherwise remain in resting position until the test is completed).*
   It is recommended that participants not be asked to answer questions for the purpose of completing study questionnaires during the MMTT.

5. Apply EMLA cream to antecubital sites as early as possible prior to venipuncture.

6. Place an I.V. line into an antecubital vein, using an intracatheter/butterfly needle (usually 20 or 22 gauge depending upon the size of the participant). *Note: The intracatheter may be kept patent between samples with a slow saline drip or heparinized saline solution (as per the guidelines of your institution) in a 20 mL syringe, injecting about 2-3 mL after each blood draw.*

7. Before the procedure, fill several 3 mL syringes with luer-lock tips with 1 mL normal saline solution to flush the adapter after each blood draw. This is only necessary if the blood sampling is more than 3 minutes apart. Write specific time points with an alcohol-proof pen on each of the tubes.

8. Obtain samples, 1.0 ml should be collected for glucose and 1.0 ml should be collected for c-peptide at each of the time points; immediately invert each tube gently 8 -10 times to mix sample, avoid jarring or shaking, then place upright on ice or in refrigerator; spin samples at approximately 1200 to 1300 x g for 10 minutes in a chilled centrifuge within 1 hour after drawing:

   a. The first sample should be taken at least 10 minutes after establishing the line(s) and when participant is calm and relaxed (if possible, depending on age) - this is the "-10 minute" sample.
   b. The second sample should be taken just prior to drinking the Boost - this is the "0 minute" sample.

c. Meal consumption - Start the clock at the beginning of the drink. The dose of Boost must be completely consumed within five (5) minutes.
d. Obtain post-meal blood samples: samples are taken at 15, 30, 60, 90, and 120 minutes after time 0

Sampling Protocol:

Time (minutes)	Glucose Sample Taken 1.2 mL gray top Oxalate/Fluoride collection tube	C-peptide Sample Taken 1.2 mL lavender top EDTA collection tube
-10	X	X
0	X	X
Drink Boost		
15	X	X
30	X	X
60	X	X
90	X	X
120	X	X

9. Termination of MMTT: test is terminated after the blood sample at 120 minutes is obtained. At that time, the indwelling cannula(e) will be withdrawn, pressure applied and a sterile strip bandage applied.

10. Upon completion of the test, bandage the blood draw site and the participant should have a snack, for example peanut butter or cheese crackers, coffee, milk or ginger ale.

11. Transfer plasma into the appropriate 1.8 mL cryovials. Screw tops on tightly to avoid leakage.
12. Store samples at -70° C. The lab has requested that sites place all of the subject's Glucose and C-peptide samples collected at one visit right next to each other in the freezer box so that the samples can be analyzed together at the lab.

MMTT Sample Collection Form

The SCFs contain constraints that prevent a vial barcode number from being saved more than once. If you try to save a vial barcode number that has already been saved, an error message will appear that explains why the new information cannot be saved. If the vial barcode number that you are trying to save is correct and the same vial barcode number has been entered (and saved) incorrectly for a subject that is within your clinical center, please try to determine the mistake that was made and correct appropriately on the TEDDY website (the Local Code, Subject ID, Visit Name and Test Name associated with the other sample will be provided in the error message) – if you are unable to make the correction yourself contact the DCC at **TEDDY@epi.usf.edu** to make the correction for you. If the

sample has already been sent to the Repository or Lab, please contact the Repository or Lab and the DCC with the correct information; once the Repository or Lab verifies that the new information you have given is correct then you should correct this information on the TEDDY website – if you are unable to make the correction yourself contact the DCC at **TEDDY@epi.usf.edu** to make the correction for you. If the vial barcode number was incorrectly entered and saved for a subject that is not within your clinical center, please contact the DCC at **TEDDY@epi.usf.edu**

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject
4. Under "Search Results", click on the Local Code of the desired subject.
5. The site should choose "Post-Diagnosis Visit MMTT Sample Collection Form" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
6. Click 'Select Form' button that is below dropdown menu.
7. Subject ID, Local Code, and Clinical Center fields will be prepopulated on the Sample Collection Form
8. Choose the visit location code from the drop down menu and enter the Date of Draw (DD/MMM/YYYY) on this form.
9. For the -10 minutes, 0 minutes, 15 minutes, 30 minutes, 60 minutes, 90 minutes and 120 minutes C-peptide and Glucose samples, indicate the type of sample (venous blood or venous plasma) and enter the time the sample was processed (this is the time the sample was placed in the freezer).
10. Find the row containing the "Test Name" (i.e. -10 minutes, 0 minutes, 15 minutes, 30 minutes, 60 minutes, 90 minutes or 120 minutes C-peptide samples; 10 minutes, 0 minutes, 15 minutes, 30 minutes, 60 minutes, 90 minutes and 120 minutes Glucose samples) of the sample in the vial you would like to scan. If an insufficient blood volume amount was obtained, and there is not enough blood for that particular Test Name, check the "Insufficient Blood Volume" Box in that row, repeat this step as necessary then continue to step 17; if there is a sufficient amount of blood go to step 11.
11. Place cursor in the "Vial Barcode Number" box in this row.
12. Scan the preprinted barcode located on the cryovial containing this particular sample.
13. In the provided space, enter the sample volume (mL) contained in the cryovial.
14. In the provided space enter box number and space number where the sample will be stored.
15. Place the cryovial in the exact freezer box and space number that you entered on the SCF for that particular sample. The lab has requested that sites place all of the subject's Glucose and C-peptide samples collected at one visit right next to each other in the freezer box so that the samples can be analyzed together at the lab.

16. Repeat steps 10-15 as necessary.
17. When all information for this specific SCF has been entered, click the "Save Form" button at the top of this form.
18. Store the samples at -70°C. Send samples to the MMTT/OGTT lab in bulk shipments on dry ice once a month. The lab has requested that sites place all of the subject's Glucose and C-peptide samples collected at one visit right next to each other in the freezer box so that the samples can be analyzed together at the lab.

Once the Participant's Details Page has been refreshed, you will see "Post-Diagnosis Visit MMTT Sample Collection Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1. Click on the form link under 'Completed Additional Study Forms'
2. A new window will open which will have a link to the "Post-Diagnosis Visit MMTT Sample Collection Form" that has been saved for this subject.
3. Click on the 'View/Edit/Print" link to open up the specific form for this subject.

Tracking System instructions for MMTT Samples

If the site is unable to collect data for the form, the site should mark a not done reason in the tracking system of the form:

1. Go to the corresponding form:
    a. Choose "Post-Diagnosis Visit MMTT Sample Collection Form" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
    b. Click 'Select Form' button that is below dropdown menu.
2. Select "Tracking System" button at top of form.
3. A new window will open which allows the site to enter the reason why the form was not completed.
4. Once the not done reason has been selected, click "Save Form".

Once the Participant's Details Page has been refreshed, you will see "Post-Diagnosis Visit MMTT Sample Collection Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1. Click on the form link under 'Completed Additional Study Forms'
2. A new window will open which will have a link to the tracking system form that has been saved for this subject.
3. Click on the 'Tracking' link to open up the specific tracking system form for this subject.

Entering information into the "Sample Shipment System"

1. Go to the "Sample Shipment System" located on the left navigational toolbar under "Data Management".
2. Enter the date of shipment.
3. If you have user access to more than one shipment origin, you will need to choose which destination the samples you are shipping are being shipped from. If you only have user access to one shipment origin, the 'Origin' drop-down menu will be defaulted to that location and you do not need to do anything.
4. Choose the "MMTT/OGTT Lab" destination option under "Select where samples will be shipped to".
5. Enter the freezer box number(s) (numbers separated by commas) that you are going to be shipping that day and click "Search".
6. The Local Code, Subject ID, Clinical Center, Test Name, Vial Barcode Number, Visit Location Code, Date Draw, Box/Pouch Number, Space Number, Sample Volume and "Delete From Shipment" option will appear for all the samples that are located in the box(es).
7. Enter the tracking number and courier service for that shipment.
8. Click on "Print and Email Shipping List". A dialog box will open that asks "Are you sure you want to print and email the shipment list?" Press 'OK' if you do and 'Cancel' if you don't.
9. Once 'OK' has been clicked an Excel file will be created that will contain information pertaining to each sample (Vial Barcode Number, Subject ID, etc).
10. Save this file for your records; an email containing this file will automatically be sent to the DCC and to the MMTT/OGTT Lab.
11. Print out a copy of this list to be shipped with the samples.
12. Repeat this process as necessary until all the boxes you will be sending that day have been entered.

Packing and Shipping Instructions:

1. Please do not ship packages on Friday. The MMTT/OGTT lab is closed for business on weekends.
2. Place the freezer box along with a STP-152 absorbent strip inside a STP-731 inner leak proof poly (plastic) bag. Seal the bag.
3. Place the poly bag inside a STP-730 envelope, fold over and tuck the STP-730 into pocket.
4. Place the STP-730 envelope in the center of the STP-309 shipper.
5. Fill the remainder of the space between the STP-730 envelope and the inner walls of the cooler with dry ice.
6. Put the lid on the cooler and place the excel printout (containing the sample information) on top of the cooler. Place the "empty packaging cover" (if included – this will be one piece of cardboard that is attached to the outside of the box) on top of the list.
7. Close and tape the outer cardboard box.

8. Attach labels to side of box with "Biological Products Diagnostic Specimens" statement:
   d. Stick the dry ice label in the upper left corner. Enter the weight of dry ice in kg on the label.
   e. Stick a separate address label in the lower left corner under the dry ice label.
   f. Don't cover the words "Diagnostic Specimens"

9. **For shipments within the United States** use the pre-printed FedEx US air bill provided to you to ship the specimens to the MMTT/OGTT Lab.
   a. In Section 1, enter the date, your name and phone number. (Sender's FedEx Account Number, Company and Address information should be already pre-printed on the air bill).
   b. Section 3, should already be pre-printed on the air bill with MMTT/OGTT Lab address

UFHPL Endocrine Lab
ATTN: Dave Pittman
4800 SW 35 Drive
Gainesville, FL 32608
(352) 265-9900
UF_TEDDY@Pathology.ufl.edu

   c. Under Section 4a, Express Package Service, mark "FedEx Standard Overnight".
   d. Complete Section 5, Packaging
   e. Complete Section 6, Special Handling:
      iii. Under "Does this shipment contain dangerous goods?" check "Yes, Shippers Declaration not required".
      iv. Check the "Dry Ice" block and enter "1" x "#" kg. This is the total weight of dry ice added to the shipping box, in kg.
   f. Under Section 7, Payment:
      i. "Sender" should be pre-marked (DCC account information is listed on the Sender section)
      ii. Enter "1" under "Total Packages".
      iii. Weigh the package and indicate the weight of the package under "Total Weight"
   g. Follow the peel and stick instructions on the back of the air bill (no document holder required).
   h. Attach the air bill to the lower right corner of the side of the box.
   i. Call FedEx at 1.800.Go.FedEx® (800.463.3339) or go to http://www.fedex.com/us/ to schedule a pick-up
   j. Attach "Biological Substance Category B" label to one side of shipping box.
   k. Fill out "Dry Ice" label and attach to one side of shipping box – include dry ice weight (kg), ship to and ship from information.

10. **For shipments within Europe** use the preprinted World House Air Way Bill (HAWB) to ship the samples to the MMTT/OGTT Lab. **PLEASE DO NOT SEND SHIPMENTS ON THURSDAY OR FRIDAY IN ORDER TO AVOID THAWING OF SAMPLES OVER THE WEEKEND.**
    a. Complete the sections of the HAWB that have not been pre-printed
    b. Affix the HAWB to the exterior of the shipper. This form is an internal tracking form used by World to identify your shipment from pick-up to delivery. When inquiring about your shipment, reference the waybill number in the top right hand corner. World Courier will provide these forms to you with shipper and consignee information pre-printed.
    c. World will send you an example Customs Invoice, you need to copy this invoice to your letterhead, fill in information for the Date, Shipper, Consignee, and estimate the amount of sample contained in the shipment (in mL) and sign.
    d. Affix the Customs Invoice to the shipper exterior.
    e. Along with the documents listed above, also give the signed Declaration Statement to the World Courier person picking up the shipment.
    f. Call World Courier Services to arrange for pick-up:
        - Finland: 9 8700 3300
        - Sweden: 8 59441 480
    g. You will need to provide the following information to the World Courier Representative:
        - DCC Account Number: 10848
        - Time of Pick-up
        - Specification of types of samples being sent
        - Number and type of boxes being shipped
        - Special Instructions: Diagnostic shipment

13.9. Annual Diabetes Risk Discussion with Parents

TEDDY families may have a change in perception of their child's diabetes risk over the passage of time. A discussion of diabetes risk should occur at least annually. This discussion will be documented at annual visits using the "Tracking Form: Symptoms of Celiac Disease" form in the Office Use Only box. Documentation will include whether or not the discussion occurred, the date it occurred and which staff member had the discussion.

13.10. Diagnosis of Type 1 Diabetes

The second primary outcome of the TEDDY study will be the development of T1DM. Diabetes will be defined using the ADA Expert committee classification (Expert Committee on the Diagnosis of Diabetes Mellitus, 1997). This classification is based on pathogenesis rather than the requirement for insulin therapy.

To diagnose diabetes, the following ADA criteria must be met on two occasions (unless criterion 4 is present). At least one plasma, serum or whole blood glucose should be measured in a local laboratory. Hyperglycemia must not be attributable to other causes (e.g. acute stress, exogenous glucocorticoid use).

1. Casual (or: Random) (any time of day without regard to time since last meal) plasma glucose >= 200 mg/dL (11.1 mmol/L), if accompanied by unequivocal symptoms (i.e. polyuria, polydipsia, polyphagia, and/or weight loss)

Or

2. Fasting (no food or drinks except water for at least 8 hours; the subject should not fast for longer than 16 hours though) plasma glucose >= 126 mg/dL (7 mmol/L)

Or

3. 2-hour plasma glucose >=200 mg/dL (11.1 mmol/L) in oral glucose tolerance test (OGTT). Glucose dose is determinant on body weight to a maximum of 75 grams. See MOO section 13.4.4. for instructions on OGTTs.

Or

4. Unequivocal hyperglycemia with acute metabolic decompensation (diabetic ketoacidosis).

Unless criterion 4 is present or the fasting glucose is >= 250 mg/dL (13.8 mmol/L) at the bedside or in the local laboratory on the day of testing, it is preferred that at least one of the two testing occasions involve an oral glucose tolerance test (OGTT). If the first criterion met is #3, i.e. by the 2-hour OGTT value, the OGTT should be repeated within 60 days. It is essential that every effort be made to obtain the necessary tests to establish the diagnosis of diabetes. Subjects will be instructed to eat a balanced diet and not to do any excessive exercises in the days leading up to the OGTT.

13.10.1. Diagnosis of Type 1 Diabetes Form

The Diagnosis of Type 1 Diabetes form should be completed as soon as possible after the subject has been diagnosed with T1DM. It is not necessary to complete a Change in Study Participation Form when a Diagnosis of Type 1 Diabetes Form has already been submitted for the subject. If a participant develops T1DM after they have withdrawn from the study a Diagnosis of Type 1 Diabetes Form should be completed.

NOTE: If the subject is diagnosed with Type 1 Diabetes after the close of the 15 year visit window, a Diagnosis of Type 1 Diabetes form should **NOT** be completed as the subject has finished the study and we are no longer collecting data from the subject.

How to get to the Diagnosis of Type 1 Diabetes Form

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject
4. Under "Search Results", click on the Local Code of the desired subject.
5. Choose "Diagnosis of Type 1 Diabetes" form that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
6. Click 'Select Form' button that is below dropdown menu.
7. Enter information (see detailed instructions below), click the Save button and close the form.
8. Once the form has been saved the subject's sub-status will change to "Enrolled (Diabetic)".

Once the Participant's Details Page has been refreshed, you will see "Diagnosis of Type 1 Diabetes" form under 'Completed Additional Study Forms' near top of Participant's Details Page:

1. Click on the form link under 'Completed Additional Study Forms'
2. A new window will open which will have a link to the "Diagnosis of Type 1 Diabetes Form" that has been saved for this subject.
3. Click on the 'View/Edit/Print" link to open up the specific form for this subject.

The Diagnosis of Type 1 Diabetes form should be completed with all information that is attainable by the TEDDY Staff. All fields with a red * are required to successfully save the form:

* Staff code of TEDDY staff member completing the form.
* Visit Location Code
* Date of Diagnosis of Type 1 Diabetes by ADA criteria (the date the TEDDY participant met the ADA criteria for diagnosis).
* Family has given permission to be contacted again (answer 'Yes', 'No' or 'Not asked') – this question is located at the bottom of the form

Sections of Diagnosis of Type 1 Diabetes Form:

- **'Date of Diagnosis of Diabetes by ADA Criteria':**
  The site should indicate the date that the diagnosis of Type 1 diabetes, by using the ADA criteria, was made.

- **‘Diabetes Diagnosis Made’:**
  In this section of the form, the site should indicate who made the Type 1 diabetes diagnosis. If a TEDDY staff member made the diagnosis, select the corresponding radio button and indicate the staff code on the form. If the diagnosis was made outside of the TEDDY clinic, select ‘Elsewhere’ and indicate the location of the diagnosis.

- **‘Medical Release’**
  The site should indicate whether or not a medical release has been obtained by selecting the ‘Yes’, ‘No’ or ‘Don’t know’ radio button.

- **‘Current Weight and Height’:**
  The site should document the subject’s current weight in kg and height in cm and the date of the measurement in DD MMM YYYY format.

- **‘Signs and/or Symptoms’:**
  The site should indicate if the child was symptomatic by selecting the ‘Yes’, ‘No’ or ‘Unknown’ radio button.

    - **‘If yes, complete the following’:**
      If the child was symptomatic the site should complete this section by providing the requested information for: Polyuria - select ‘yes’, ‘no’ or ‘unknown’; if yes to Polyuria indicate the date of onset; Polydipsia - select ‘yes’, ‘no’ or ‘unknown’; if yes to Polydipsia indicate the date of onset; Polyphagia - select ‘yes’, ‘no’ or ‘unknown’; if yes to Polyphagia indicate the date of onset; and Weight Loss - select ‘yes’, ‘no’ or ‘unknown’; if yes to weight loss the site should indicate the amount in kg.

- **‘Glucose Values’:**
  In this section the site should report the glucose values at the two occasions required to establish the diagnosis of Type 1 diabetes. Meter readings must be supported by at least one diagnostic laboratory sample, drawn at a different time than the meter read sample.

  The site should document the following information for each glucose value:
  - The glucose result in either:
    - mg/dL
    - mmol/L
  - Date of the result in DD MMM YYYY format
  - Hours since last meal or mark ‘unknown’
  - Type of reading – one of the following choices should be selected:
    - Meter (glucometer)
    - TEDDY lab
    - Other Lab (outside lab reading)

- Type of test – one of the following choices should be selected:
  - Random Glucose: measure of blood glucose regardless of when the participant last ate.
  - Fasting Glucose: measure of blood glucose after not eating or drinking, except for water, for at least 8 hours.
  - Postprandial Glucose: measure of blood glucose 1-2 hours after a meal.
  - OGTT (2 hour value): measure of blood glucose 2 hours after glucose drink.
- Draw site – one of the following choices should be selected:
  - Venous plasma
  - Venous blood
  - Capillary blood

- **'Glycosylated hemoglobin':**
  The site should document the result of the hemoglobin A1c either in % or mmol/mol, the date of the hemoglobin A1c measurement in DD MMM YYYY format and the normal range of the hemoglobin A1c% in this section. If the measurement was not done, the site should mark "Not Done". If the site has exhausted all efforts to obtain the information, but has been unable to, the site should mark "Subject's medical chart not available to TEDDY staff".

- **'Laboratory Values':**
  The site should report as much of the laboratory values information that is available. The 'Laboratory Values' section of the form is broken up into two parts – 'Initial Values at time of Diabetes Diagnosis' and 'pH and Bicarbonate Values at time of nadir'. If the measurement was not done, the site should mark "Not Done". If the site has exhausted all efforts to obtain the information, but has been unable to, the site should mark "Subject's medical chart not available to TEDDY staff".

  'Initial Values at time of Diabetes Diagnosis'- the site should indicate the following information applying to the time of Type 1 diabetes diagnosis:
  - Date the sample was collected that was used to obtain the initial laboratory values at the time of Type 1 diabetes diagnosis in DD MMM YYYY format
  - pH:
    - Type of sample that the pH result at the time of Type 1 diabetes diagnosis was obtained from:
      - Venous
      - Arterial
      - Capillary
    - pH result at the time of Type 1 diabetes diagnosis
    - Time the sample was collected that was used to obtain the pH value at the time of Type 1 diabetes diagnosis
      - Hours and minutes should be recorded

        - Time should be recorded in Universal Time – for example 2:00 pm would be recorded as 14:00
- Bicarbonate/total CO_2:
    - Bicarbonate/total CO_2 value at the time of Type 1 diabetes diagnosis - results should be indicated in either:
        - mEq/L
        - mmol/L
    - Time the sample was collected that was used to obtain the Bicarbonate/total CO_2 value at the time of Type 1 diabetes diagnosis
        - Hours and minutes should be recorded
        - Time should be recorded in Universal Time – for example 2:00 pm would be recorded as 14:00
- pCO_2:
    - pCO_2 value at the time of Type 1 diabetes diagnosis - results should be indicated in either:
        - torr
        - kPa
        - mmHg
    - Time the sample was collected that was used to obtain the pCO_2 value at the time of Type 1 diabetes diagnosis
        - Hours and minutes should be recorded
        - Time should be recorded in Universal Time – for example 2:00 pm would be recorded as 14:00
- Base deficit:
    - Base deficit value at the time of Type 1 diabetes diagnosis - results should be indicated in either:
        - mEq/L
        - mmol/L
    - Time the sample was collected that was used to obtain the Base deficit value at the time of Type 1 diabetes diagnosis
        - Hours and minutes should be recorded
        - Time should be recorded in Universal Time – for example 2:00 pm would be recorded as 14:00

- Base excess (BE):
    - Base excess value at the time of Type 1 diabetes diagnosis - results should be indicated in mmol/L and indicate whether negative or positive
    - Time the sample was collected that was used to obtain the Base excess value at the time of Type 1 diabetes diagnosis
        - Hours and minutes should be recorded
        - Time should be recorded in Universal Time – for example 2:00 pm would be recorded as 14:00
- Potassium:
    - Potassium value at the time of Type 1 diabetes diagnosis - results should be indicated in mmol/L

- Time the sample was collected that was used to obtain Potassium value at the time of Type 1 diabetes diagnosis
  - Hours and minutes should be recorded
  - Time should be recorded in Universal Time – for example 2:00 pm would be recorded as 14:00

- Sodium:
  - Sodium value at the time of Type 1 diabetes diagnosis - results should be indicated in mmol/L
  - Time the sample was collected that was used to obtain Sodium value at the time of Type 1 diabetes diagnosis
    - Hours and minutes should be recorded
    - Time should be recorded in Universal Time – for example 2:00 pm would be recorded as 14:00
- Chloride:
  - Chloride value at the time of Type 1 diabetes diagnosis - results should be indicated in mmol/L
  - Time the sample was collected that was used to obtain Chloride value at the time of Type 1 diabetes diagnosis
    - Hours and minutes should be recorded
    - Time should be recorded in Universal Time – for example 2:00 pm would be recorded as 14:00
- BUN:
  - BUN value at the time of Type 1 diabetes diagnosis - results should be indicated in either:
    - mg/dL
    - mmol/L
  - Time the sample was collected that was used to obtain BUN value at the time of Type 1 diabetes diagnosis
    - Hours and minutes should be recorded
    - Time should be recorded in Universal Time – for example 2:00 pm would be recorded as 14:00
- Plasma Creatinine:
  - Plasma Creatinine value at the time of Type 1 diabetes diagnosis - results should be indicated in micromol/L
  - Time the sample was collected that was used to obtain Plasma Creatinine value at the time of Type 1 diabetes diagnosis
    - Hours and minutes should be recorded
    - Time should be recorded in Universal Time – for example 2:00 pm would be recorded as 14:00
- Beta OHB (blood ketone levels):
  - Type of sample that the Beta OHB result at the time of Type 1 diabetes diagnosis was obtained from:
    - Blood
    - Serum
    - Plasma

- Beta OHB value at the time of Type 1 diabetes diagnosis - results should be indicated in either:
  - mg/dL
  - mmol/L
- Time the sample was collected that was used to obtain Beta OHB value at the time of Type 1 diabetes diagnosis
  - Hours and minutes should be recorded
  - Time should be recorded in Universal Time – for example 2:00 pm would be recorded as 14:00

- Urine Ketones:
  - Urine Ketones result at the time of Type 1 diabetes diagnosis:
    - Negative
    - Trace
    - Small
    - Moderate
    - Large
  - Time the sample was collected that was used to obtain the Urine Ketones result at the time of Type 1 diabetes diagnosis
    - Hours and minutes should be recorded
    - Time should be recorded in Universal Time – for example 2:00 pm would be recorded as 14:00
- If laboratory evaluations were not obtained to evaluate for ketoacidosis, please comment on the subject's clinical situation at diagnosis in the free-text box provided on the form.

'pH and bicarbonate values at time of nadir' – the sites should indicate the following information applying to the time of nadir. Nadir is defined as "Time at which pH or bicarbonate value is the lowest during the evaluation and treatment of the child with new onset diabetes."

- pH:
  - Type of sample that the pH result at the time of nadir was obtained from:
    - Venous
    - Arterial
    - Capillary
  - pH result at the time of nadir
  - Date the sample was collected that was used to obtain the pH value at the time of nadir in DD MMM YYYY format
  - Time the sample was collected that was used to obtain the pH value at the time of nadir
    - Hours and minutes should be recorded
    - Time should be recorded in Universal Time – for example 2:00 pm would be recorded as 14:00
- Bicarbonate:

- Bicarbonate value at the time of nadir - results should be indicated in either:
  - mEq/L
  - mmol/L
- Date the sample was collected that was used to obtain the Bicarbonate value at the time of nadir in DD MMM YYYY format
- Time the sample was collected that was used to obtain the Bicarbonate value at the time of nadir
  - Hours and minutes should be recorded
  - Time should be recorded in Universal Time – for example 2:00 pm would be recorded as 14:00

- **'Treatment'**:
  The site should indicate if the child was hospitalized by selecting the 'Yes', 'No' or 'Unknown' radio button. If the child was hospitalized, the site should indicate the name and address of the facility where the child was admitted. If the child was hospitalized the site should indicate any additional diagnoses (other than Type 1 diabetes) from the hospital discharge summary and date of admission and date of discharge. Diagnoses should be reported by using the appropriate ICD-10 code.

  The site should indicate if the child was treated in the emergency room only by selecting the 'Yes', 'No' or 'Unknown' radio button. If the child was only treated in the emergency room, the site should indicate the name and address of the emergency room, the date of the emergency room admission and the date of the emergency room discharge in DD MMM YYYY format.

  The site should indicate if the child was treated in an outpatient clinic only by selecting the 'Yes', 'No' or 'Unknown' radio button. If the child was only treated in an outpatient clinic, the site should, indicate the name and address of the clinic and the date of the initial visit in DD MMM YYYY format..

- **'Insulin':**
  The site should include information on the subject's insulin therapy in this section, including IV and/or S.C. (subcutaneous) injection. The site should indicate if insulin therapy has been started for the subject by selecting the 'Yes', 'No' or 'Unknown' radio button. If the subject has started insulin therapy, the site should indicate the date insulin therapy was started in DD MMM YYYY format.

13.10.2. Additional TEDDY Clinic Visit after Diagnosis of Type 1 Diabetes in order to Collect Data and Biological Samples at the Final End-point

TEDDY families will be informed that they should contact a TEDDY staff member to arrange an additional TEDDY visit should the TEDDY child develop T1DM in between TEDDY visits. This visit should be organized as soon as possible (within 6 weeks is strongly preferred; if it is not possible to schedule the visit until after 6 weeks diagnosis this will be accepted and the visit should be conducted at that time). The post diagnosis of T1DM visit should include the same age-appropriate procedures as a regular TEDDY visit would (e.g. clinical sample collection, extraction of data from the TEDDY book, administration of TEDDY Study questionnaires*) and the Diabetes Management Form and Final Study questionnaires. If possible previous missed DNA samples (4 year non-HLA genotyping sample and/or 6 year DNA storage sample) should be collected. If an Update form for Family History Questionnaire has not been completed within the last two years, the next due Update form should also be completed. Sites participating in the JDRF follow-up Study should complete a 7 time-point MMTT if possible and Quality of Life Questionnaires** should also be completed (JDRF recruitment ended December 31, 2016). The families will also be asked to collect an additional stool sample as soon as possible (within 7 days) after the diagnosis of T1DM using the standard TEDDY stool sample collection and shipment protocols. An additional stool sample will also be collected within 7 days after the post-diagnosis visit. NOTE: All stool sample collections on all subjects were stopped in August 2018.

If diabetes is diagnosed by abnormal glucose values or OGTT results at a routine TEDDY visit an additional visit will be scheduled within 6 weeks of the diagnosis (6 weeks is strongly preferred; if it is not possible to schedule the visit until after 6 weeks diagnosis this will be accepted and the visit should be conducted at that time). If the subject is diagnosed with diabetes at the 15 year visit, there will be no additional visit as the 15 year visit is the last visit of the study; the site should complete the Diagnosis of Type 1 Diabetes form and the Diabetes Management Form at the 15 year visit. The post diagnosis of T1DM visit (if subject diagnosed at any other visit other than the 15 year visit) will include the same age-appropriate procedures as a regular TEDDY visit would (e.g. clinical sample collection, extraction of data from the TEDDY book, administration of TEDDY Study questionnaires*) and the Diabetes Management Form and Final Study questionnaires. If possible previous missed DNA samples (4 year non-HLA genotyping sample and/or 6 year DNA storage sample) should be collected. If an Update form for Family History Questionnaire has not been completed within the last two years, the next due Update form should also be completed. Sites participating in the JDRF follow-up Study should complete a 7 time-point MMTT should be completed and if possible a Diabetes Management Form should also be completed and if possible Quality of Life Questionnaires* should also be completed (JDRF recruitment ended December 31, 2016). The families will be asked to collect an additional stool sample as soon as possible (within 7 days) after

the diagnosis of T1DM using the standard TEDDY stool sample collection and shipment protocols and an additional stool sample will also be collected within 7 days after the post-diagnosis visit. NOTE: All stool sample collections on all subjects were stopped in August 2018.

*If an Annual Questionnaire is due, this form should not be given at the post-diagnosis TEDDY visit.

** The Quality of Life Questionnaires consist of the following forms listed below. Sites should refer to the JDRF follow-up study MOO for further information on these questionnaires. The Quality of Life Questionnaires to be completed at the TEDDY post-diagnosis visit can be found under the "Additional Study Forms" drop-down on the TEDDY Participants' Details Page:

1. PedsQL for parents
2. PedsQL for children ages 8 and older
3. STAI and Well-Being for parents
4. STAI for children ages 8 and older
5. Pediatric Inventory for Parents (PIP)

This final visit will be the "official" end-point for the child's participation in the TEDDY Study and will offer an opportunity for psychological support to the family.

The data should then be entered in the corresponding online SCFs and forms/questionnaires. Stool samples that are collected post-diagnosis will be assigned to a visit number based upon the sample's date of collection, just as is done for regularly collected stool samples. NOTE: All stool sample collections on all subjects were stopped in August 2018.

At the time of data entry, if the window for a sample collected or a form/questionnaire completed at the post-diagnosis TEDDY visit is no longer in the future, but the actual date of collection or date of form completion is still outside of the allotted window, the Clinical Center should enter the data on the corresponding form and enter a date of collection/interview date/review date that falls within the window so that the form can be saved. Once the Clinical Center has entered the information they should contact the DCC with the correct date of collection/interview date/review date so that the DCC can update the date in its database. The Clinical Center should email the following information to the DCC when making this request:

- Subject ID
- Local Code

- Sample name(s), visit(s) and correct date(s) of collection for sample(s) collected at post-diagnosis visit
- Form name(s), visit(s) and correct interview date(s)/review date(s) for form(s)/questionnaire(s) completed at post-diagnosis visit

If a window has not yet opened (the window consists of future dates) for a sample collected or a form/questionnaire completed at the post-diagnosis TEDDY visit, the Clinical Center should contact the DCC to open the window so that the data can be entered. The Clinical Center should email the following information to the DCC when making this request:

- Subject ID
- Local Code
- Sample name(s), visit(s) and correct date(s) of collection for sample(s) collected at post-diagnosis visit
- Form name(s), visit(s) and correct interview date(s)/review date(s) for form(s)/questionnaire(s) completed at post-diagnosis visit

The DCC will notify the site when the window has been changed and they are able to enter the data. The site should immediately enter the data and let the DCC know when the data entry has been completed so that the window can be immediately changed back.

Sites should mark all errors associated with this window change in the Error Reporting and Verification System (ERVS) as verified.

At the time of analysis, it will be known that the sample(s) and form(s)/questionnaire(s) were collected at the post-diagnosis visit based upon the date of diabetes diagnosis and the date of collection of the sample(s)/completion of the form.

13.10.3. Diabetes Management Form

The Diabetes Management Form is designed to be completed at the TEDDY post-diagnosis visit and can be found under the "Additional Study Forms" drop-down menu.

13.10.3.1. Content areas of the Diabetes Management Form

The Diabetes Management Form collects information on:

- Participant's means of glucose monitoring.
- The number of times the participant checks their blood glucose levels daily.
- Blood glucose records for a 2 week period prior to visit.

  - If sites are unable to collect blood glucose records from a 2 week period, data should be collected for whatever time period is available. Data fields for "Date of first recorded blood glucose monitoring for questions below" and "Date of last recorded blood glucose monitoring for questions below" have been added to the form so that sites can indicate the length of the actual collection period.
- Insulin dose and type information for a 3 day period prior to visit.
- Incidences of hypoglycemia participant experienced since last visit.

13.10.3.2. Administration of the Diabetes Management Form

During the post-diagnosis visit, study staff will complete the Diabetes Management Form with the primary caretaker.

- Questions are to be read to the primary caretaker directly from the Diabetes Management Form.
- No items should be skipped.
- If a participant refuses a question, the interviewer should so note on the interview form, initial and date.
- In the US, care should be taken to enter all dates correctly in the European format: day, month/year.
- The Diabetes Management Form, section B "Glucose" question #4 asks for "Lowest recorded glucose" and question #5 asks for "Highest recorded glucose". When a glucose reading meets a certain threshold it will either display as "Low" or "High" on the meter rather than as a numerical value. Listed below are the various meters' thresholds and the numerical value that should be indicated for these questions on the Diabetes Management Form for these situations:
  - Contour Next, Contour Link, Contour XT
    - "LOW" reading should be indicated as 10.91 mg/dL or 0.6 mmol/L on the Diabetes Management Form
    - "HIGH" reading should be indicated as 605.45 mg/dL or 33.3 mmol/L on the Diabetes Management Form
  - Contour USB Next
    - "LOW" reading should be indicated as 20 mg/dL or 1.1 mmol/L on the Diabetes Management Form
    - "HIGH" reading should be indicated as 605.45 mg/dL or 33.3 mmol/L on the Diabetes Management Form
  - Dexcom (all devices)
    - "LOW" reading should be indicated as 39 mg/dL or 2.16 mmol/L on the Diabetes Management Form

    - "HIGH" reading should be indicated as 401 mg/dL or 22.26 mmol/L on the Diabetes Management Form
- FreeStyle Freedom Lite
    - "LOW" reading should be indicated as 19 mg/dL or 1.06 mmol/L on the Diabetes Management Form
    - "HIGH" reading should be indicated as 501 mg/dL or 27.8 mmol/L on the Diabetes Management Form
- OneTouch UltraEasy
    - "LOW" reading should be indicated as 18 mg/dL or 1.00 mmol/L on the Diabetes Management Form
    - "HIGH" reading should be indicated as 602 mg/dL or 33.4 mmol/L on the Diabetes Management Form
- OneTouch UltraMini
    - "LOW" reading should be indicated as 19 mg/dL or 1.06 mmol/L on the Diabetes Management Form
    - "HIGH" reading should be indicated as 601 mg/dL or 33.39 mmol/L on the Diabetes Management Form
- OneTouch Ultra2
    - "LOW" reading should be indicated as 69 mg/dL or 3.83 mmol/L on the Diabetes Management Form
    - "HIGH" reading should be indicated as 601 mg/dL or 33.39 mmol/L on the Diabetes Management Form
- Nano AccuCheck
    - "LOW" reading should be indicated as 19 mg/dL or 1.06 mmol/L on the Diabetes Management Form
    - "HIGH" reading should be indicated as 601 mg/dL or 33.39 mmol/L on the Diabetes Management Form

- The Diabetes Management Form, section C asks about Insulin use:
    - When short acting insulin is given intermittently:
        - The site should calculate the average/day for the short acting insulin from the usage over the last 3 days for question #2.
        - The site should document the short acting insulin as an insulin type that the child uses under question #4.
- The Diabetes Management Form asks for data on hypoglycemia since the last visit in section D of the form. At the post-diagnosis visit the questions in section D should be answered since diagnosis.

13.11. Diagnosis of Non-Type 1 Diabetes Form

The "Diagnosis of Non-Type 1 Diabetes" form should be completed when a subject is diagnosed with some other type of diabetes other than Type 1, such as Type 2, MODY, CFRD, etc. The form should be completed with all information that is attainable by the TEDDY Staff. All fields with a red * are required to successfully save the form.

How to get to the Diagnosis of Non-Type 1 Diabetes Form

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject.
4. Under "Search Results", click on the Local Code of the desired subject.
5. Choose "Diagnosis of Non-Type 1 Diabetes" form that is in the "Additional Study Forms" dropdown menu at the upper right-hand corner of the Participant's Details Page.
6. Click 'Select Form' button that is below dropdown menu.
7. Enter information, click the Save button and close the form.

Once the Participant's Details Page has been refreshed, you will see "Diagnosis of non-Type 1 Diabetes" form under 'Completed Additional Study Forms' near top of Participant's Details Page:

1. Click on the form link under 'Completed Additional Study Forms'
2. A new window will open which will have a link to the "Diagnosis of Non-Type 1 Diabetes Form" that has been saved for this subject.
3. Click on the 'View/Edit/Print" link to open up the specific form for this subject.

13.12. Reward

Physical rewards or "prizes" may be beneficial in promoting a positive attitude of the study by both adults and children. Rewards can be utilized in accordance with site regulations but should never be used as coercion to participate. Age appropriate prizes such as stickers, cars, bubbles, books etc. can be given at the end of the visit. Prizes should never be held back because of an unsuccessful blood draw or difficult behavior.

13.13. Preparation for Future Visits

It may be beneficial for the child to discuss the procedures after completion. The child should be encouraged to verbalize their feelings; staff may need to give the child "permission" to identify feelings, i.e., "That might have been scary."

If age appropriate, have children write a note to themselves that will be kept in the chart to review for the next visit, i.e., "It didn't hurt."

13.14. Adverse events

Adverse events may occur with any procedure at any time. Staff should be aware of potential problems and be prepared. Adverse events are reported to the Principal Investigator of each TEDDY Clinical Center and to the Data Coordinating Center.

Children react to blood draws and procedures differently than adults and are usually unable to verbalize feeling light headed or nauseous. Careful observation of their behavior will allow identifying a problem is occurring and allow intervention to prevent injury.

- Observe the skin for allergic reaction to the EMLA cream, remove immediately and observe child for worsening symptoms.
- Observe breathing during procedures, watch for breath holding and encourage them to "breathe".
- Children may be becoming nauseated when they begin to lick their lips and swallow frequently. Have equipment (trash cans) handy in case of vomiting.
- Children may be becoming light headed, observe for yawning; this is an attempt at self vagal stimulation. Be prepared to lay them down and elevate their feet without locking the knees. Cool cloths on the back of the neck or forehead may be helpful.
- If the child does lose consciousness, lay them down, elevate their feet without locking the knees, and be prepared for vomiting when they regain consciousness. Some children will display mild neurological symptoms when losing consciousness, i.e., positioning, slight shaking, moaning; explain to parents that these symptoms are not unusual and will pass quickly.
- Keep the child in observation after an adverse event until staff and parents agree and feel comfortable with the child leaving. The Principal Investigator/MD may need to examine the child. Juice or crackers may be helpful (if not nauseated) with recuperation.

Parents/primary caretakers may express concerns about the study, procedures or staff. All questions and concerns are to be addressed honestly and calmly, recognize when a supervisor or Principal Investigator should be involved.

Needle sticks: Follow your institutions guidelines, policies and procedures in the event of a needle stick.

13.15. Maternal blood sample

A maternal blood sample will be obtained by the 24 month visit if:

- The mother has type 1, type 2, or had gestational diabetes with this pregnancy

OR

- The child is shown to be islet autoantibody positive before the 9 month visit

Venipuncture Procedures

a. Explain the procedure to the mother.
b. Wash your hands with soap and water and put on a pair of disposable plastic latex gloves.
c. Make sure the participant's arm is in a flat and stable position.
d. Identify the best vein possible.
e. Once venipuncture site has been determined, apply tourniquet. If drawing from the hand, apply the tourniquet to the wrist proximal to the wrist bone and curve the hand in a secure hold. If the antecubital vein is most optimal, apply tourniquet 2 inches above site and secure entire arm. A well applied tourniquet will slow venous blood return, causing veins to distend. It will not block arterial blood supply, so pulses distal to the tourniquet should still be palpable and the limb should not blanch. PRECAUTIONS: The tourniquet should be left on the minimal amount of time necessary for an adequate amount of blood to be obtained.
f. Make certain the site extremity remains secure and still. The arm should be extended but not hyper extended from the body.
g. Cleanse venipuncture site with an alcohol wipe, using circular motion toward the periphery. Allow area to dry before proceeding. This prevents the burning sensation for patients when venipuncture is performed and it prevents hemolysis of the blood.
h. Hold the syringe attached to the butterfly in the dominant hand or lay the syringe next to the parent's arm. Hold the wing portion of the needle between the thumb and the index finger while pulling the skin over the knuckles for the dorsal hand site or toward the wrist for the antecubital site.
i. Insert the needle at a 10 to 15 degree angle, ensuring the needle bevel is face up and parallel to the vein. Use a straight stab; do not poke around. A flash or small amount of blood will appear in the tubing when the needle is successfully in the vein.
j. Secure the needle in the vein by holding it with the thumb of the opposite hand. Slowly draw the blood in the attached syringe in a downward position, making certain that the needle remains secure.
k. When adequate blood (approximately 3mL) is obtained, remove the tourniquet.
l. Remove the needle quickly and immediately apply gentle pressure to the site with the gauze pad or cotton ball.
m. Activate the safety device feature on the needle to prevent an unnecessary needle stick. Remove and discard the butterfly needle set up.
n. Have the parent keep arm fully extended and elevated. Have them apply pressure over puncture site for a few minutes.

o. Check site for bleeding. If site is still bleeding, continue direct pressure. If site has stopped bleeding, apply bandage to venipuncture site.
p. Invert SST tube to mix thoroughly, 5-10 times.
q. The SST tube will be allowed to clot at room temperature and then centrifuged (800 x g for 20 minutes) to separate the serum from the clot.
r. The serum will then be aliquoted into externally threaded plastic cryovials as stated below. Serum should be transferred in such a way that possible contamination is avoided. Please use disposable Pasteur pipettes.
s. Aliquot at least **0.1 mL** of serum into a 0.5 mL cryovial with a **red** cap insert for the Maternal Autoantibody Reference Lab Sample that will be sent to the Autoantibody Reference Lab; Aliquot at least **0.1 mL** of serum into a 0.5 mL cryovial with a **red** cap insert for the Maternal Autoantibody Repository Sample that will be sent to the Repository;
t. Dispose of butterfly and other contaminated materials in sharp box, throw away materials not used, remove gloves, and wash hands.

The blood drawing procedure is usually the most uncomfortable and stressful part of the clinic visit for all parties involved. It is recommended that the timing of this event take place after all other data collection is complete.

13.16. Water Samples

The family will need to bring the first water sample to the 9-month visit, make sure to review the procedure with them and provide the necessary equipment at the 6-month visit.

Subsequent water samples will be collected by the family every two years at the annual visit for ages 3 years, 5 years, 7 years, etc. through the life of the study. Make sure to review the collection procedure with the family and provide the necessary equipment at the visit preceding each of these collections. The site should stress the importance to the family of making sure not to fill the vial with water past the 1.8 ml mark.

> **NOTE**: Even if the parent indicates that the child has never received any water the Diet Committee would still like the water sample collected.

Equipment

a. Two - 2 ml collection tubes
b. Sample box or Ziploc bag to hold tubes

Family Instructions

We would like to get a sample of the water from your house that you give to your baby most often. This is the water your baby gets in a bottle or is mixed with infant formula, cereal, or juice. This might be tap water, bottled water, distilled water, or water from your refrigerator. Choose the type of water your child gets most often. If

you normally boil, distill, or filter the water, follow your normal routine for this sample as well. Please allow boiled water to cool prior to filling the collection tubes. **Please collect the sample the morning of your 9 month visit *(note to staff: replace with 3 year visit, 5 year visit, etc. as necessary)* and bring it with you to the clinic.**

a. Take two collection tubes to your water source and remove the caps. Find the 1.8 line on the collection tubes.
b. If you are collecting water from your tap, adjust the water flow for ease of collection. From other sources, like a refrigerator, it may be necessary to first put the water in a glass or measuring cup and then fill the tubes.
c. Fill each of thetwo tubes to the 1.8 line on the side of the tube. (Please make sure not to fill past the 1.8 line; we will be freezing these samples and if the water is filled past this line there is not enough room for expansion.)
d. Secure caps on the tubes. Place the tubes in the box Ziploc bag provided note the date and water source below and bring to the 9-month clinic visit.
e. Examine the Ziploc bag to make sure that both tubes are filled to the fill line, their caps are securely fastened, and there is no leakage.

At Visit Procedure – Water Sample Collection Form

The SCFs contain constraints that prevent a vial barcode number from being saved more than once. If you try to save a vial barcode number that has already been saved, an error message will appear that explains why the new information cannot be saved. If the vial barcode number that you are trying to save is correct and the same vial barcode number has been entered (and saved) incorrectly for a subject that is within your clinical center, please try to determine the mistake that was made and correct appropriately on the TEDDY website (the Local Code, Subject ID, Visit Name and Test Name associated with the other sample will be provided in the error message) – if you are unable to make the correction yourself contact the DCC at **TEDDY@epi.usf.edu** to make the correction for you. If the sample has already been sent to the Repository or Lab, please contact the Repository or Lab and the DCC with the correct information; once the Repository or Lab verifies that the new information you have given is correct then you should correct this information on the TEDDY website – if you are unable to make the correction yourself contact the DCC at **TEDDY@epi.usf.edu** to make the correction for you. If the vial barcode number was incorrectly entered and saved for a subject that is not within your clinical center, please contact the DCC at **TEDDY@epi.usf.edu**

> **NOTE WELL – *This information below pertains to water collections prior to March 2019; starting in March 2019 only two vials of water were collected at each time point***:
> For this event to be considered completed, the family must provide a minimum of **three** water vials filled to the fill line. This represents the smallest amount of water needed to perform lab analyses for TEDDY.

If the family has provided fewer than three vials, please first of all, thank the family for their efforts. Then instruct the family that more water is needed next time, and ask the provider to bring in **six** new vials for the next planned TEDDY visit (for example 12-month visit, 39 month visit, 66 month visit, etc). Also remember to replenish the supply of empty water vials for the provider prior to the end of the TEDDY visit.

Enter cryovial information onto the SCFs (as instructed below) for all water samples brought back to the clinical center by the family (even if less than 3 cryovials were brought back).

If the family brings in three, four, five or six new vials of water to the next TEDDY visit as requested above, the one or two vials of water that the family brought to the previous visit can be discarded and the corresponding vial information can be cleared from the Water SCF and replaced with the newly collected water sample vial information. If the family does not bring in three, four, five or six new vials of water the one or two vials of water that were originally submitted will be kept.

There are two ways to retrieve the subject's Water Sample Collection Form, please see instructions below.

"Sample Collection Form" link

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Sample Collection Form" link under "Data Management" on the left navigational toolbar.
3. Enter both the Subject ID and Local Code of the subject.
4. Select the desired visit.
5. Select the desired Sample Collection Form (i.e. water).
6. Subject ID, Local Code, and Clinical Center fields will be prepopulated on the Sample Collection Form.
7. Choose the correct Visit Location Code from the drop down menu - this is the location where the TEDDY visit took place. Drop-down list based upon TEDDY Clinical Center field.
8. Enter the Date of Collection of the water sample (DD/MMM/YYYY).
9. Select that the water sample is "Household water" – which is per protocol. If a non-household water sample was previously collected and entered for a subject indicate that it is "Non-household water" by following the instructions below for "Non-household water samples (non-protocol)")
10. Choose the type of water sample:
    - Tap water from city
    - Tap water from well or spring
    - Tap water, unknown source
    - Bottled water
    - Other

11. Indicate whether or not the water sample was filtered, boiled and/or distilled.
12. If the water samples were stored at room temperature for 72 hours or longer, mark the checkbox "Samples have been stored at room temperature for 72 hours or longer".
13. Find the row containing the "Test Name" (i.e. water) of the sample in the vial you would like to scan. If not all of the vials were brought back in by the family, check the "Not Collected" box in that row. Repeat this step as necessary then go to step 17; otherwise go to step 14.
14. Place cursor in the "Vial Barcode Number" box in this row.
15. Scan the preprinted barcode located on the cryovial containing this particular sample.
16. In the provided spaces enter the sample volume and box number and space number where the sample will be stored.
17. Repeat steps 12-16 with the other cryovial containing the water sample.
18. Click the Save button.

"Enter/Edit/View" Link

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject.
4. Under "Search Results", click on the Local Code of the desired subject.
5. Choose the desired Sample Collection Form by clicking on the links under "Event Title" (i.e. Water Sample)
6. Subject ID, Local Code, and Clinical Center fields will be prepopulated on the Sample Collection Form.
7. Choose the correct Visit Location Code from the drop down menu - this is the location where the TEDDY visit took place. Drop-down list based upon TEDDY Clinical Center field.
8. Enter the Date of Collection of the water sample (DD/MMM/YYYY).
9. Select that the water sample is "Household water" – which is per protocol. If a non-household water sample was previously collected and entered for a subject indicate that it is "Non-household water" by following the instructions below for "Non-household water samples (non-protocol)")
10. Choose the type of water sample:
    Tap water from city
    Tap water from well or spring
    Tap water, unknown source
    Bottled water
    Other

11. Indicate whether or not the water sample was filtered, boiled and/or distilled.
12. If the water samples were stored at room temperature for 72 hours or longer, mark the checkbox "Samples have been stored at room temperature for 72 hours or longer".
13. Find the row containing the "Test Name" (i.e. water) of the sample in the vial you would like to scan. If not all of the vials were brought back in by the family, check the "Not Collected" box in that row. Repeat this step as necessary then go to step 17; otherwise go to step 14.
14. Place cursor in the "Vial Barcode Number" box in this row.
15. Scan the preprinted barcode located on the cryovial containing this particular sample.
16. In the provided spaces enter the sample volume and box number and space number where the sample will be stored.
17. Repeat steps 12-16 with the other cryovial containing the water sample.
18. Click the Save button.

Non-household water samples (non-protocol)

Radio buttons have been added to the Water SCFs for "Household water" and "Non-household water" due to the collection of non-protocol water samples at some sites (non-household samples). If a water sample has been collected that is from 'non-household' water:

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject.
4. Under "Search Results", click on the Local Code of the desired subject.
5. Choose the desired Sample Collection Form by clicking on the links under "Event Title" (i.e. Water Sample).
6. Select that the water sample is "Non-household water".
7. A dialogue box will pop-up that says "By selecting "non-household" water the current water collection samples will become unusable and you will be asked to re-enter the water sample collection form. Do you want to continue?" and you will be given the options of "OK" or "Cancel".
8. After clicking "OK" the vials in that SCF will be flagged in the DCC's database as 'unusable' due to being non-protocol samples.
9. A blank water SCF will appear on the screen. You can fill in the information for the newly collected household water samples at that time or you can enter the vial information at a later time.

10. Note – once you close out the SCF you will need to refresh the Participant's Details Page (PDP) in order for the old water SCF to be cleared from the current PDP. You will no longer be able to access the water SCF with the 'non-household water' sample information.
11. Once the water SCF has been resaved as "non-household water" an automatic email will be sent to you and the DCC. The email will contain information on the vials that were marked as 'non-protocol non-household water samples'.

Storage

Water sample may be stored at room temperature, while protected from direct sunlight, for up to 72 hours before freezing at -70°C. Before freezing the site should check each vial to make sure that it has not been filled past the 1.8 ml mark; if the vial contains water past the 1.8 ml mark, the site should remove the excess water before freezing the sample. At the time samples are readied for shipment to the Repository, a second check should occur that looks for compromised tubes and/or caps coming off due to freezing. The frozen water samples will be batched and mailed to the repository for storage.

Shipping: Water samples shipped to Repository

Entering information into the "Sample Shipment System"

Once a month each clinical center will send bulk shipments of water samples to the NIDDK Repository.

1. Logon to the TEDDY website, http://teddy.epi.usf.edu/
2. Go to the "Sample Shipment System" located on the left navigational toolbar under "Data Management".
3. Enter the date of shipment.
4. If you have user access to more than one shipment origin, you will need to choose which destination the samples you are shipping are being shipped from. If you only have user access to one shipment origin, the 'Origin' drop-down menu will be defaulted to that location and you do not need to do anything.
5. Choose the "Repository" destination option under "Select where samples will be shipped to".
6. Enter the box number for each box that you are going to be shipping (numbers separated by commas) and click "Search".
7. The Local Code, Subject ID, Clinical Center, Test Name, Vial Barcode Number, Visit Location Code, Date Draw, Box/Pouch Number, Space Number, Sample Volume, Site Number (this will only appear for samples being shipped to the Repository) and "Delete From Shipment" option will be filled in for all the samples that are located in that box.
8. Enter the tracking number and courier service for that shipment and any comments you would like to notify the lab about.

9. Click on "Print and Email Shipping List". A dialog box will open that asks "Are you sure you want to print and email the shipment list?" Press 'OK' if you do and 'Cancel' if you don't.
10. Once 'OK' has been clicked an Excel file will be created that will contain information pertaining to each sample (Vial Barcode Number, Subject ID, etc).
11. Save this file for your records; an email containing this file will automatically be sent to the DCC and to the Repository.
12. Print out a copy of this list to be shipped with the samples.
13. Repeat this process as necessary until all of the boxes you will be sending that day have been entered.

Packing and Shipping Instructions for US Sites:

1. Please do not ship packages on Friday. The repository is closed for business on weekends.
2. Place the 2" freezer box (NOTE: WATER SAMPLES CAN BE SENT IN BULK SHIPMENTS WITH THE BLOOD SAMPLES THAT ARE BEING SHIPPED TO THE REPOSITORY) along with a STP-152 absorbent strip inside a STP-711 inner leak proof poly (plastic) bag. Seal the bag.
3. Place the poly bag inside a STP-714 envelope, fold over and tuck the STP-714 into pocket.
4. Place up to three filled STP-714 envelopes in the cardboard inner box, tape the box shut and place it in the middle of the cooler in the STP-320 shipper. If there are only one or two vial boxes in the shipment, fill the rest of the space inside the cardboard inner box with packing material (e.g. bubble wrap or newspaper) to prevent movement during shipment.
5. Fill the remainder of the space between the cardboard box and the inner walls of the cooler with dry ice.
6. Put the lid on the cooler and place the excel printout (containing the sample information) on top of the cooler. Place the "empty packaging cover" (if included – this will be one piece of cardboard that is attached to the outside of the box) on top of the list.
7. Close and tape the outer cardboard box.
8. Attach labels to side of box with "Biological Products Diagnostic Specimens" statement:
   a. Stick the Class 9 dry ice label in the upper left corner (of the SIDE of the box). Enter the weight of dry ice as 8 kg.
   b. Stick a separate address label in the lower left corner, under the dry ice label, that reads:

Chris Deigan
Disease Prevention
Fisher BioServices
20301 Century Blvd.
Building 6, Suite 400

c. Stick the "UN3373 Diagnostic Specimens" label to the right of the dry ice label.

9. Use the pre-printed FedEx US air bill to ship the samples to the Fisher/NIDDK Biosample Repository.
   a. In Section 1, enter the date, your name, return address and phone number. Leave "Sender's FedEx Account Number" blank
   b. Complete Section 6, Special Handling:
      i. Under "Does this shipment contain dangerous goods?" check "Yes, Shippers Declaration not required".
      ii. Check the "Dry Ice" block and enter "1" x "8" kg.
   c. Under Section 7, Payment:
      i. Enter "1" under "Total Packages".
      ii. Enter "24 lbs" under "Total Weight" (this is the total weight if the shipper contains 3 freezer boxes with 81 samples in each).
   d. Follow the peel and stick instructions on the back of the air bill (no document holder required).
   e. Attach the air bill to the lower right corner of the side of the box.
10. Call FedEx at 1.800.Go.FedEx® (800.463.3339) **or** go http://www.fedex.com/us/ to schedule a pick-up
11. Notify the repository of the incoming shipment and tracking number via email (BIO-NIDDKRepository@FisherSci.com) or fax (301-515-4049) on the day the package is picked up by FedEx.

Packing and Shipping Instructions for European Sites:

1. Place the 2" freezer box (NOTE: WATER SAMPLES CAN BE SENT IN BULK SHIPMENTS WITH THE BLOOD SAMPLES THAT ARE BEING SHIPPED TO THE REPOSITORY) along with an absorbent strip inside the inner leak proof poly (plastic) bag. Seal the bag.
2. Place the plastic bag inside the long Tyvek envelope. Place the box inside the far end of the long pocket of the envelope. Crease the envelope near the middle, fold the envelope over, and place the end of the envelope containing the box inside the short pocket on the opposite side of the envelope. Push the box firmly into the short end of the envelope.
3. Put a layer of dry ice in the bottom of the box. Place up to 5 Tyvek envelopes containing boxes on the dry ice.
4. Fill the remainder of the space in the shipper with dry ice up to about four inches from the top.
5. Put the foam insert on top of the dry ice in the opening. Place a copy of the manifest shipping form inside a zip-lock bag, and set it on top of the foam insert under the lid flaps.
6. Close and tape the cardboard box.
7. Attach all labels to the same side of the box:
   a. Stick the dry ice label on the side of the box in the upper right corner. Enter the weight of dry ice as 14 kg.

b. Place the "UN3373 Diagnostic Specimens" label on the top, center, to the left of the dry ice label.
c. Stick the small address label below the "Up" arrows that reads:

Chris Deigan
Disease Prevention
Fisher BioServices
20301 Century Blvd.
Building 6, Suite 400
Germantown MD 20874
USA

8. Use the preprinted World House Air Way Bill (HAWB) to ship the samples to the Fisher/NIDDK Biosample Repository.
9. Complete the sections of the HAWB that have not been pre-printed
10. Affix the HAWB to the exterior of the shipper. This form is an internal tracking form used by World to identify your shipment from pick-up to delivery. When inquiring about your shipment, reference the waybill number in the top right hand corner. World Courier will provide these forms to you with shipper and consignee information pre-printed.
11. World will send you an example Customs Invoice, you need to copy this invoice to your letterhead, fill in information for the Date, Shipper, Consignee, and estimate the amount of sample contained in the shipment (in mL) and sign.
12. Affix the Customs Invoice to the shipper exterior
13. Along with the documents listed above, also give the signed Declaration Statement to the World Courier person picking up the shipment.
    - Call World Courier Services to arrange for pick-up:
    - Finland: 9 8700 3300
    - Germany: 89 9698 9290
    - Sweden: 8 59441 480

    You will need to provide the following information to the World Courier Representative:
    - Study Account Number
    - Time of Pick-up
    - Specification of types of samples being sent
    - Number and type of boxes being shipped
    - Special Instructions: Diagnostic shipment.
14. Notify the repository by email (BIO-NIDDKRepository@FisherSci.com) of an incoming shipment on the day the package is picked up by World. Provide the tracking number, so the repository may track the shipment if it is delayed.

Contingency Plan for Missing Water Sample:
In the event that a water sample is not brought to the visit at which it is required (for example 9-month visit, 36 month visit, 60 month visit, etc) we will request one at the next planned visit, as identified in the follow-up schedule listed in the protocol (for example 12 month visit, 39 month visit, 66 month visit, etc).

NOTE: While all attempts should be made to collect the water sample from the parent at the required visit or the next planned visit, the Diet Committee will still accept water samples collected beyond the next planned visit. For these rare instances (when the water sample has been collected outside of the window) the Clinical Center should enter the sample information on the corresponding Sample Collection Form and enter a date of collection that falls within the window so that the Sample Collection Form can be saved. Once the Clinical Center has entered the information they should contact the DCC with the correct date of collection so that the DCC can update the date of collection in its database. The Clinical Center should email the following information to the DCC when making this request:

- Subject ID
- Local Code
- Sample name, visit and correct date of collection for water samples collected outside of the window

At the time of analysis these samples will be flagged as being collected outside of the window and it will be left to the discretion of the Diet Committee to decide whether or not they would like to analyze these samples.

NOTE – *This information below pertains to water collections prior to March 2019; starting in March 2019 only two vials of water were collected at each time point*:
For this event to be considered completed, the family must provide a minimum of **three** water vials filled to the fill line. This represents the smallest amount of water needed to perform lab analyses for TEDDY.

If the family has provided fewer than three vials, please first of all, thank the family for their efforts. Then instruct the family that more water is needed next time, and ask the provider to bring in **six** new vials for the next planned TEDDY visit (for example 12-month visit, 39 month visit, 66 month visit, etc). Also remember to replenish the supply of empty water vials for the provider prior to the end of the TEDDY visit.

Enter cryovial information onto the SCFs (as instructed above) for all water samples brought back to the clinical center by the family (even if less than 3 cryovials were brought back).

If the family brings in three, four, five or six new vials of water to the next TEDDY visit as requested above, the one or two vials of water that the family brought to the previous visit can be discarded and the corresponding vial information can be cleared from the Water SCF and replaced with the newly collected water sample vial information. If the family does not bring in three, four, five or six new vials of water the one or two vials of water that were originally submitted will be kept.

13.17. Toenail Samples

Pre-Visit Preparation

a. Toenails will be collected beginning at the 24 month visit and then every 1 year after that. In the event that the visit that the toenail sample should be collected at is missed (24 month, 48 month, 6 year, etc.) or the TEDDY staff members are unable to collect the sample at this time, the sample can either be collected at the next visit in the TEDDY schedule (27 month, 51 month (if child is on 3 month visit schedule) or 54 month (if child is on 6 month visit schedule), 6 year 3 month (if child is on 3 month visit schedule) or 6 year 6 month (if child is on 6 month visit schedule), etc.) or another option is for the parent to collect the toenail sample at home and mail into the TEDDY clinic (see appendix D for parent toenail collection instructions).

   NOTE: While all attempts should be made to collect the toenail sample at the required visit or the next planned visit, the Diet Committee will still accept toenail samples collected beyond the next planned visit. For these rare instances (when the toenail sample has been collected outside of the window) the Clinical Center should enter the sample information on the corresponding Sample Collection Form and enter a date of collection that falls within the window so that the Sample Collection Form can be saved. Once the Clinical Center has entered the information they should contact the DCC with the correct date of collection so that the DCC can update the date of collection in its database. The Clinical Center should email the following information to the DCC when making this request:

   - Subject ID
   - Local Code
   - Sample name, visit and correct date of collection for toenail sample collected outside of the window

   At the time of analysis these samples will be flagged as being collected outside of the window and it will be left to the discretion of the Diet Committee to decide whether or not they would like to analyze these samples.

b. Send pre-visit preparation instructions to parent prior to the visit that the toenail sample will be collected at (see appendix C for pre-visit preparation instructions):
c. Ask parents to refrain from trimming toenails for 3 weeks before the visit. Note: children's thumbnails grow at rate of about 0.7 mm per week with significant interindividual variation
d. Cosmetic nail polish should be removed with a commercial polish remover before the visit

At Visit Procedure

a. Please only collect toenail samples, do NOT collect fingernail samples.
b. Remove nail polish if not already done.
c. Gently scrape debris from below the toenails with an orange stick or soft tipped cuticle stick (i.e. clean under the baby's nails).
d. Cleanse top of toenails with ethanol or propanol (rubbing alcohol).
e. Place a clean lab pad under the child's feet to catch the trimmings. Trim all ten toenails to a comfortable length using either a clipper or nail scissors. Trim mostly straight across, and leave some white edge visible. Do not trim below the nail groove.
f. Clinical centers should get as much toenail sample as possible, but at least 3 pieces of toenail should be obtained for the sample to be considered sufficient. If 3 pieces of toenail cannot be obtained at the visit that the toenail sample is to be collected at (24 month, 48 month, 6 year, etc.) then the clinical center should wait until the next visit in the TEDDY schedule (27 month, 51 month (if child is on 3 month visit schedule) or 54 month (if child is on 6 month visit schedule), 6 year 3 month (if child is on 3 month visit schedule) or 6 year 6 month (if child is on 6 month visit schedule), etc.) to obtain the toenail sample. Toenail samples taken at two different visits should NOT be combined in order to achieve the required amount of 3 pieces.
g. Place clippings in etched 2 mL screw-cap cryovial provided.
h. Go to the subject's "Toenail Sample Collection Form" - there are two ways to retrieve the subject's Sample Collection Form:

Toenail Sample Collection Form

The SCFs contain constraints that prevent a vial barcode number from being saved more than once. If you try to save a vial barcode number that has already been saved, an error message will appear that explains why the new information cannot be saved. If the vial barcode number that you are trying to save is correct and the same vial barcode number has been entered (and saved) incorrectly for a subject that is within your clinical center, please try to determine the mistake that was made and correct appropriately on the TEDDY website (the Local Code, Subject ID, Visit Name and Test Name associated with the other sample will be provided in the error message) – if you are unable to make the correction yourself contact the DCC at **TEDDY@epi.usf.edu** to make the correction for you. If the sample has already been sent to the Repository or Lab, please contact the Repository or Lab and the DCC with the correct information; once the Repository or Lab verifies that the new information you have given is correct then you should correct this information on the TEDDY website – if you are unable to make the correction yourself contact the DCC at **TEDDY@epi.usf.edu** to make the correction for you. If the vial barcode number was incorrectly entered and saved for a subject that is not within your clinical center, please contact the DCC at **TEDDY@epi.usf.edu**

There are two ways to retrieve the subject's Toenail Sample Collection Form, please see instructions below.

"Sample Collection Form" link

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Sample Collection Form" link under "Data Management" on the left navigational toolbar.
3. Enter both the Subject ID and Local Code of the subject.
4. Select the desired visit.
5. Select the desired Sample Collection Form (i.e. toenail).
6. Subject ID, Local Code, and Clinical Center fields will be prepopulated on the Sample Collection Form.
7. Choose the correct Visit Location Code from the drop down menu - this is the location where the TEDDY visit took place. Drop-down list based upon TEDDY Clinical Center field.
8. Enter the Date of Collection of the toenail sample (DD/MMM/YYYY).
9. Find the row containing the "Test Name" (i.e. toenail) of the sample in the vial you would like to scan. Place cursor in the "Vial Barcode Number" box in this row.
10. Scan the preprinted barcode located on the cryovial containing this particular sample.
11. In the provided space enter box number and space number where the sample will be stored.
12. Click the Save button.

"Enter/Edit/View" Link

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject.
4. Under "Search Results", click on the Local Code of the desired subject.
5. Choose the desired Sample Collection Form by clicking on the links under "Event Title" (i.e. Toenail Sample)
6. Subject ID, Local Code, and Clinical Center fields will be prepopulated on the Sample Collection Form.
7. Choose the correct Visit Location Code from the drop down menu - this is the location where the TEDDY visit took place. Drop-down list based upon TEDDY Clinical Center field.
8. Enter the Date of Collection of the toenail sample (DD/MMM/YYYY).
9. Find the row containing the "Test Name" (i.e. toenail) of the sample in the vial you would like to scan. Place cursor in the "Vial Barcode Number" box in this row.
10. Scan the preprinted barcode located on the cryovial containing this particular sample.

11. In the provided space enter box number and space number where the sample will be stored.
12. Click the Save button.

Storage

Toenails may be stored in the -70°C freezer for up to 1 month before being mailed to the repository for storage.

Shipping: Toenail samples shipped to Repository

Entering information into the "Sample Shipment System"

Once a month each clinical center will send bulk shipments of toenail samples to the NIDDK Repository.

1. Logon to the TEDDY website, http://teddy.epi.usf.edu/
2. Go to the "Sample Shipment System" located on the left navigational toolbar under "Data Management".
3. Enter the date of shipment.
4. If you have user access to more than one shipment origin, you will need to choose which destination the samples you are shipping are being shipped from. If you only have user access to one shipment origin, the 'Origin' drop-down menu will be defaulted to that location and you do not need to do anything.
5. Choose the "Repository" destination option under "Select where samples will be shipped to".
6. Enter the box number for each box that you are going to be shipping (numbers separated by commas) and click "Search".
7. The Local Code, Subject ID, Clinical Center, Test Name, Vial Barcode Number, Visit Location Code, Date Draw, Box/Pouch Number, Space Number, Sample Volume, Site Number (this will only appear for samples being shipped to the Repository) and "Delete From Shipment" option will be filled in for all the samples that are located in that box.
8. Enter the tracking number and courier service for that shipment and any comments you would like to notify the lab about.
9. Click on "Print and Email Shipping List". A dialog box will open that asks "Are you sure you want to print and email the shipment list?" Press 'OK' if you do and 'Cancel' if you don't.
10. Once 'OK' has been clicked an Excel file will be created that will contain information pertaining to each sample (Vial Barcode Number, Subject ID, etc).
11. Save this file for your records; an email containing this file will automatically be sent to the DCC and to the Repository.
12. Print out a copy of this list to be shipped with the samples.
13. Repeat this process as necessary until all the boxes you will be sending that day have been entered.

Packing and Shipping Instructions for US Sites:

1. Please do not ship packages on Friday. The repository is closed for business on weekends.
2. Place the 2" freezer box along with a STP-152 absorbent strip inside a STP-711 inner leak proof poly (plastic) bag. Seal the bag.
3. Place the poly bag inside a STP-714 envelope, fold over and tuck the STP-714 into pocket.
4. Place up to three filled STP-714 envelopes in the cardboard inner box, tape the box shut and place it in the middle of the cooler in the STP-320 shipper. If there are only one or two vial boxes in the shipment, fill the rest of the space inside the cardboard inner box with packing material (e.g. bubble wrap or newspaper) to prevent movement during shipment.
5. Fill the remainder of the space between the cardboard box and the inner walls of the cooler with dry ice.
6. Put the lid on the cooler and place the excel printout (containing the sample information) on top of the cooler. Place the "empty packaging cover" (if included – this will be one piece of cardboard that is attached to the outside of the box) on top of the list.
7. Close and tape the outer cardboard box.
8. Attach labels to side of box with "Biological Products Diagnostic Specimens" statement:
    a. Stick the Class 9 dry ice label in the upper left corner (of the SIDE of the box). Enter the weight of dry ice as 8 kg.
    b. Stick a separate address label in the lower left corner, under the dry ice label, that reads:

        Chris Deigan
        Disease Prevention
        Fisher BioServices
        20301 Century Blvd.
        Building 6, Suite 400
        Germantown MD 20874
        USA

    c. Stick the "UN3373 Diagnostic Specimens" label to the right of the dry ice label.
9. Use the pre-printed FedEx US air bill to ship the samples to the Fisher/NIDDK Biosample Repository.
    a. In Section 1, enter the date, your name, return address and phone number. Leave "Sender's FedEx Account Number" blank
    b. Complete Section 6, Special Handling:
        i. Under "Does this shipment contain dangerous goods?" check "Yes, Shippers Declaration not required".
        ii. Check the "Dry Ice" block and enter "1" x "8" kg.
    c. Under Section 7, Payment:
10. Enter "1" under "Total Packages".

11. Enter "24 lbs" under "Total Weight" (this is the total weight if the shipper contains 3 freezer boxes with 81 samples in each).
12. Follow the peel and stick instructions on the back of the air bill (no document holder required).
    i. Attach the air bill to the lower right corner of the side of the
    ii. box.
13. Call FedEx at 1.800.Go.FedEx® (800.463.3339) **or** go http://www.fedex.com/us/ to schedule a pick-up
14. Notify the repository of the incoming shipment and tracking number via email (BIO-NIDDKRepository@FisherSci.com) or fax (301-515-4049) on the day the package is picked up by FedEx.

Packing and Shipping Instructions for European Sites:

1. Place the 2" freezer box along with an absorbent strip inside the inner leak proof poly (plastic) bag. Seal the bag.
2. Place the plastic bag inside the long Tyvek envelope. Place the box inside the far end of the long pocket of the envelope. Crease the envelope near the middle, fold the envelope over, and place the end of the envelope containing the box inside the short pocket on the opposite side of the envelope. Push the box firmly into the short end of the envelope.
3. Put a layer of dry ice in the bottom of the box. Place up to 5 Tyvek envelopes containing boxes on the dry ice.
4. Fill the remainder of the space in the shipper with dry ice up to about four inches from the top.
5. Put the foam insert on top of the dry ice in the opening. Place a copy of the manifest shipping form inside a zip-lock bag, and set it on top of the foam insert under the lid flaps.
6. Close and tape the cardboard box.
7. Attach all labels to the same side of the box:
    a. Stick the dry ice label on the side of the box in the upper right corner. Enter the weight of dry ice as 14 kg.
    b. Place the "UN3373 Diagnostic Specimens" label on the top, center, to the left of the dry ice label.
    c. Stick the small address label below the "Up" arrows that reads:

       Chris Deigan
       Disease Prevention
       Fisher BioServices
       20301 Century Blvd.
       Building 6, Suite 400
       Germantown MD 20874
8. **USA** Use the preprinted World House Air Way Bill (HAWB) to ship the samples to the Fisher/NIDDK Biosample Repository.
9. Complete the sections of the HAWB that have not been pre-printed
10. Affix the HAWB to the exterior of the shipper. This form is an internal tracking form used by World to identify your shipment from pick-up to delivery. When inquiring about your shipment, reference the waybill

number in the top right hand corner. World Courier will provide these forms to you with shipper and consignee information pre-printed.

11. World will send you an example Customs Invoice, you need to copy this invoice to your letterhead, fill in information for the Date, Shipper, Consignee, and estimate the amount of sample contained in the shipment (in mL) and sign.
12. Affix the Customs Invoice to the shipper exterior
13. Along with the documents listed above, also give the signed Declaration Statement to the World Courier person picking up the shipment.
14. Call World Courier Services to arrange for pick-up:
    - Finland: 9 8700 3300
    - Germany: 89 9698 9290
    - Sweden: 8 59441 480

    You will need to provide the following information to the World Courier Representative:
    - Study Account Number
    - Time of Pick-up
    - Specification of types of samples being sent
    - Number and type of boxes being shipped
    - Special Instructions: Diagnostic shipment.
15. Notify the repository by email (BIO-NIDDKRepository@FisherSci.com) of an incoming shipment on the day the package is picked up by World. Provide the tracking number, so the repository may track the shipment if it is delayed.

13.18. Salivary Cortisol Samples

Frequently Asked Questions: Salivary Cortisol Sample Collection

- A family rescheduled after salivary cortisol sample #1 was collected. The family was asked to re-collect the #1 sample using the last 2 sorbettes of the 5 sorbette pack. Can 1 or 2 sorbettes be collected or does it always have to be 3? IT IS OKAY TO COLLECT 2 SORBETTES AS LONG AS THE INSTRUCTIONS ARE FOLLOWED FOR COLLECTING THE SAMPLE(S)
- Hurricane spray was used on a child instead of EMLA. The question "Time when numbing cream (EMLA etc.) was applied" is asked when the family arrives at their visit. The Hurricane spray was applied within 1 minute of the blood draw. What time should be entered? The time they arrived at their visit or the time the numbing agent was applied? THE TIME THE NUMBING AGENT WAS APPLIED
- A morning salivary cortisol sample brought into clinic was spun but no saliva was available. What is the recommendation for the #2 and #3 sample collections? COLLECT #2 AND #3 AND ASK THE FAMILY TO SEND #1 WITHIN 7 DAYS
- What is the window for having #1 sample collected and sent to the clinic if it is not collected on the day of the clinic visit**?** 7 DAYS
- If the #1 sample is not received within the 7 day window, should the other two samples be discarded? NO - DO NOT DISCARD THE SAMPLES

- If a parent brings in a morning salivary cortisol sample that doesn't meet the criteria (no food or drink, except water for 30 minutes before sample taken in AM), does TEDDY keep the sample? YES – KEEP THE SAMPLE AND BE SURE TO RECORD WHAT HAPPENED ON THE FORM (COLLECTION OF SALIVA – PARENT FORM)
  In this case should we have a record of this noted on the sample collection form? NO – DOES NOT NEED TO BE INDICATED ON SCF
  If we keep these samples, will we always need to be sorting samples based on quality of collection? NO
- What should happen if the child has eaten or drank something in the 30 minutes before the 1st in-clinic pre-blood draw salivary cortisol sample? Should we get the sample or not get the sample knowing it was compromised. It is not too hard to imagine that kids will eat something on the way to the clinic. Also, having them wait an additional 30 minutes to meet this requirement is not feasible. YES – GET THE SAMPLE AND NOTE FOOD OR DRINK WAS CONSUMED
- Between the 1st and 2nd in-clinic salivary cortisol sample collections there are children who receive their usual lollipop or food treat for having completed the blood draw. There is no place to note this on the form and the clinic staff is unsure if they should have collected the salivary cortisol sample or not, given that they were not done properly. Does the form need more places to note these issues and decisions? COLLECT THE SAMPLE, BUT IT IS IMPORTANT FOR THE STAFF TO BE SURE THAT NO FOOD OR DRINK (BESIDES WATER) ARE CONSUMED BETWEEN THE 2 CLINIC SALIVA COLLECTIONS (the committee did not think it was necessary to add a place to note this on the form)
- Should clinic staff have the children routinely rinse before collection of each in-clinic salivary cortisol sample as a matter of protocol? THE MOO STATES: "THE CHILD SHOULD RINSE HIS/HER MOUTH OUT WITH WATER BEFORE THE PRE-BLOOD DRAW SALIVA COLLECTION." FOR THE 2ND CLINIC COLLECTION, THEY SHOULD RINSE ONLY IF FOOD OR DRINK WAS CONSUMED.
- Should a salivary cortisol sample be collected if an OGTT is done at the same visit? NO – THE SALIVA SHOULD BE COLLECTED AT THE NEXT VISIT.

Salivary cortisol will be used as a biomarker of the child's overall stress level (morning cortisol) and the child's reaction to a standardized stressor (the TEDDY visit's blood draw) to the TEDDY protocol. This biomarker will permit a more definitive test of: (1) psychological stress as a possible trigger of persistent beta-cell autoimmunity and progression to TID, and (2) psychological stress and increased susceptibility to illness which, in turn, may increase the child's risk for autoimmunity and T1D.

There will be three annual salivary cortisol collections from each subject at 3.5 years, 4.5 years, and 5.5 years of age. The window for the 3.5 year sample collection is any time during the child's third year. Similarly, the window for the 4.5 year sample collection is any time during the child's fourth year and the window for the 5.5 year sample collection is any time during the child's fifth year. The saliva collection at home and at the TEDDY clinic visit should be completed at the same time or close to the time that the CBCL is filled out.

Each of the annual collections will consist of collecting three salivary samples. The first of the three samples should be collected by the child's parent at home 30 minutes after the child wakes on the morning the TEDDY child comes into the clinic (ideally we want the morning cortisol sample to be collected on the same day of the TEDDY visit, however if this is not possible, the Psychosocial committee will accept a morning cortisol sample collected within 1 week of the TEDDY visit; instruct the parent to keep the morning cortisol sample at room temperature and to not refrigerate it). Parents will be provided with a salivary cortisol kit and instructions on how to collect the cortisol sample (see Appendix E) at the previous visit or the kit and instructions will be sent home by mail before the next visit. If the cortisol kit is given out at the previous visit a reminder card should be sent home or a reminder call given prior to the upcoming visit. Parents will collect the sample by using three Sorbettes (cotton pads on a stick). The parent will bring the morning saliva collection with them to the TEDDY visit along with the completed "Collection of Saliva – Parent Form". Should any of the 3.5, 4.5 or 5.5 year visits be missed, the morning saliva sample should still be collected and sent to the TEDDY Clinical Center along with the completed "Collection of Saliva – Parent Form".

When the child comes to the TEDDY visit, two salivary cortisol samples will be collected: a "baseline" assessment immediately prior to the blood draw (or blood draw attempt) and a "post-stress" assessment, 20 minutes after the blood draw (20 minutes from when the needle goes in or blood draw attempt). Salivary samples will be collected with three Sorbettes (cotton pads on a stick) and the TEDDY staff member should complete the "Collection of Saliva – Staff Form". Immediately after the blood draw (or blood draw attempt), during the 20 minute waiting period between saliva collections, it is recommended that the child be given a coloring book or some other play activity. In Germany, if children are on the Long_Distance protocol, the parent will collect the morning saliva and the two saliva samples before and after the blood draw (or blood draw attempt) and will complete both Collection of Saliva forms. Parents will receive a reminder and instruction call from a TEDDY staff member.

> **NOTE**: If a blood draw is not attempted at the visit, Salivary Cortisol samples should not be collected because the blood draw is the standardized stressor.

> **NOTE**: If the window has closed for the Cortisol sample and a blood draw was not attempted at any of the visits within the Cortisol window, the Psychosocial committee would like you to keep the morning cortisol sample collected by the parent (because it can be used for other analyses) and enter the data associated with this sample on the SCF.

Prior to the pre-blood draw saliva collection, parents should provide information on the time the child woke up in the morning. Study staff or parents (if they are on the Long-Distance protocol) should note the time of the saliva collections and blood draw (or blood draw attempt) on the "Collection of Saliva – Staff Form". Parents should

also confirm the child is not on oral steroids (topical or inhaled steroids are ok) and has NOT had caffeinated drinks before the clinic visit, milk or food within 30 minutes before the pre-blood draw saliva collection. If food or drink has been consumed within these time intervals, the site may wait the necessary time interval before conducting the saliva collection, or re-schedule the visit.

The child should rinse his/her mouth out with water before the pre-blood draw saliva collection. If the child needs more than one stick to get the blood sample (or more than one stick for the attempt to get the blood sample), this should be noted. The second, post-blood draw saliva collection should occur 20 minutes after the second attempt.

Instructions for collecting salivary cortisol samples:

NOTE: It is very important that the site develop a system to keep track of which vial contains the sample that was collected at home, which vial contains the baseline sample that was collected immediately prior to the blood draw and which vial contains the sample collected 20 minutes after the blood draw. A suggested method is writing a #1 on the vial that contains the sample that was collected at home, writing a #2 on the vial that contains the baseline sample that was collected immediately prior to the blood draw and writing a #3 on the vial that contains the sample collected 20 minutes after the blood draw.

1. Remove one Sorbette from the envelope. Close the envelope immediately to protect the other Sorbettes from contact with moisture.
2. Place the cap of the conical tube on a flat surface.
3. Place and hold the Sorbette under the child's tongue for at least 40 seconds. Pull out the Sorbette a bit and replace it under the tongue again until the Sorbette begins to expand (at least one minute total time). **It is very important that you hold the Sorbette firmly the whole time when you collect the saliva to avoid swallowing of the Sorbette.** The Sorbette can also be moved around in the mouth and lip area to collect saliva that may be drooling down the cheek or pooling in the mouth.
4. When the Sorbette is saturated, insert it tip down into the cap.
5. Place the second Sorbette under the child's tongue and repeat steps 3-4 above.
6. Place the third Sorbette under the child's tongue and repeat step 3-4 above.
7. Slide the conical storage tube over the purple Sorbette sticks and snap down securely into cap. **It is critical that the saliva collected via Sorbette not evaporate. Make sure the cap is placed tightly on the tube.**
8. Samples that have been collected at home by the parent should be brought to the TEDDY clinic visit. Samples that have been collected via the Long-Distance protocol should be sent immediately in a pre-paid shipping box to the TEDDY Clinical Center.

9. TEDDY Clinical Centers should place the tubes cap side up in the freezer box and refrigerate samples as soon as possible.

Instructions for processing salivary cortisol samples:

1. Before freezing occurs, the saliva should be centrifuged out of the Sorbettes by the TEDDY Clinical Center.
2. Spin samples at approximately 1500 x g for 15 minutes.
3. After spinning has been completed, remove the Sorbette with tweezers.
4. Place cap tightly on tube containing the saliva sample and place the tubes cap side up in the freezer box.
5. Freeze the saliva samples at -70°C.

Salivary Cortisol Sample Collection Form

The SCFs contain constraints that prevent a vial barcode number from being saved more than once. If you try to save a vial barcode number that has already been saved, an error message will appear that explains why the new information cannot be saved. If the vial barcode number that you are trying to save is correct and the same vial barcode number has been entered (and saved) incorrectly for a subject that is within your clinical center, please try to determine the mistake that was made and correct appropriately on the TEDDY website (the Local Code, Subject ID, Visit Name and Test Name associated with the other sample will be provided in the error message) – if you are unable to make the correction yourself contact the DCC at **TEDDY@epi.usf.edu** to make the correction for you. If the sample has already been sent to the Repository or Lab, please contact the Repository or Lab and the DCC with the correct information; once the Repository or Lab verifies that the new information you have given is correct then you should correct this information on the TEDDY website – if you are unable to make the correction yourself contact the DCC at **TEDDY@epi.usf.edu** to make the correction for you. If the vial barcode number was incorrectly entered and saved for a subject that is not within your clinical center, please contact the DCC at **TEDDY@epi.usf.edu**

There are two ways to retrieve the subject's Cortisol Sample Collection Form, please see instructions below.

"Sample Collection Form" link

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Sample Collection Form" link under "Data Management" on the left navigational toolbar.
3. Enter both the Subject ID and Local Code of the subject.
4. Select the desired visit.
5. Select the desired Sample Collection Form (i.e. cortisol).

6. Subject ID, Local Code, and Clinical Center fields will be prepopulated on the Sample Collection Form.
7. Choose the correct Visit Location Code from the drop down menu - this is the location where the TEDDY visit took place. Drop-down list based upon TEDDY Clinical Center field.
8. **If the cortisol sample(s) was processed according to standard TEDDY protocol** (i.e. the Long-Distance protocol was not followed):
   a. Mark the "Sample processed according to standard protocol or Standard protocol followed, insufficient volume" and continue to step 9.

   If the cortisol sample(s) was processed according to the Long-Distance protocol:
   b. Indicate the date and time that the sample was processed (this is the time the sample was put in the freezer) and continue to step 9.
9. In the first grid box below the "Use with Remote Protocol Only" box, find the row containing the "Test Name" (i.e. Salivary Cortisol Sample #1 (sample collected at home 30 minutes after child wakes); Salivary Cortisol Sample #2 (sample collected prior to blood draw or blood draw attempt); Salivary Cortisol Sample #3 (sample collected 20 minutes after blood draw or blood draw attempt) of the sample in the vial you would like to scan.
10. In the provided space enter the number of sorbettes in the tube.
11. In the provided space enter the Date of Collection of the sample in the tube (DD/MMM/YYYY).
12. In the provided space enter the time the sample in the tube was collected. Time must be entered in universal time, for example 2:00 pm would be recorded as 14:00.
13. Repeat steps 9-12 as necessary.
14. In the second grid box below the "Use with Remote Protocol Only" box, find the row containing the "Test Name" (i.e. Salivary Cortisol Sample #1 (sample collected at home 30 minutes after child wakes); Salivary Cortisol Sample #2 (sample collected prior to blood draw or blood draw attempt); Salivary Cortisol Sample #3 (sample collected 20 minutes after blood draw or blood draw attempt) of the sample in the vial you would like to scan. If a sample was not collected for a particular Test Name, check the "Not Collected" Box in that row, repeat this step as necessary then continue to step 21; if a sample was collected go to step 15.
15. Place cursor in the "Vial Barcode Number" box.
16. Scan the preprinted barcode located on the cryovial containing this particular sample.
17. Enter the sample volume (mL) contained in the cryovial in the provided space.
18. In the provided spaces enter box number and space number where the sample will be stored.
19. Place the cryovial in the exact freezer box and space number that you entered on the SCF for that particular sample.

20. Repeat steps 14-19 as necessary.
21. When all samples for this specific SCF have been entered, click the "Save Form" button.

"Enter/Edit/View" Link

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject.
4. Under "Search Results", click on the Local Code of the desired subject.
5. Choose the desired Sample Collection Form by clicking on the links under "Event Title" (i.e. Cortisol Sample)
6. Subject ID, Local Code, and Clinical Center fields will be prepopulated on the Sample Collection Form.
7. Choose the correct Visit Location Code from the drop down menu - this is the location where the TEDDY visit took place. Drop-down list based upon TEDDY Clinical Center field.
8. **If the cortisol sample(s) was processed according to standard TEDDY protocol** (i.e. the Long-Distance protocol was not followed):
   a. Mark the "Sample processed according to standard protocol or Standard protocol followed, insufficient volume" and continue to step 9.

   If the cortisol sample(s) was processed according to the Long-Distance protocol:
   a. Indicate the date and time that the sample was processed (this is the time the sample was put in the freezer) and continue to step 9.
9. In the first grid box below the "Use with Remote Protocol Only" box, find the row containing the "Test Name" (i.e. Salivary Cortisol Sample #1 (sample collected at home 30 minutes after child wakes); Salivary Cortisol Sample #2 (sample collected prior to blood draw or blood draw attempt); Salivary Cortisol Sample #3 (sample collected 20 minutes after blood draw or blood draw attempt) of the sample in the vial you would like to scan.
10. In the provided space enter the number of sorbettes in the tube.
11. In the provided space enter the Date of Collection of the sample in the tube (DD/MMM/YYYY).
12. In the provided space enter the time the sample in the tube was collected. Time must be entered in universal time, for example 2:00 pm would be recorded as 14:00.
13. Repeat steps 9-12 as necessary.
14. In the second grid box below the "Use with Remote Protocol Only" box, find the row containing the "Test Name" (i.e. Salivary Cortisol Sample #1 (sample collected at home 30 minutes after child wakes); Salivary Cortisol Sample #2 (sample collected prior to blood draw or blood draw attempt); Salivary Cortisol Sample #3 (sample collected 20 minutes after blood draw or blood draw attempt) of the sample in the vial you would like to

scan. If a sample was not collected for a particular Test Name, check the "Not Collected" Box in that row, repeat this step as necessary then continue to step 21; if a sample was collected go to step 15.

15. Place cursor in the "Vial Barcode Number" box.
16. Scan the preprinted barcode located on the cryovial containing this particular sample.
17. Enter the sample volume (mL) contained in the cryovial in the provided space.
18. In the provided spaces enter box number and space number where the sample will be stored.
19. Place the cryovial in the exact freezer box and space number that you entered on the SCF for that particular sample.
20. Repeat steps 14-19 as necessary.
21. When all samples for this specific SCF have been entered, click the "Save Form" button

Collection of Saliva – Parent Form

The "Collection of Saliva – Parent Form" contains the saliva collection instructions for the parent as well as the form that the parent should complete and bring to the TEDDY clinic visit along with the saliva sample that was collected at home. The "Collection of Saliva – Parent Form" can be accessed through the "Enter/Edit/View" link:

"Enter/Edit/View" Link

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject.
4. Under "Search Results", click on the Local Code of the desired subject.
5. Choose the "Collection of Saliva – Parent Form" by clicking on the link under "Event Title"

Collection of Saliva – Staff Form

The "Collection of Saliva – Staff Form" should be completed by the TEDDY staff member on the day of the collection of the saliva sample at the TEDDY clinic. The "Collection of Saliva – Staff Form" can be accessed through the "Enter/Edit/View" link:

"Enter/Edit/View" Link

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject.
4. Under "Search Results", click on the Local Code of the desired subject.

5. Choose the "Collection of Saliva – Parent Form" by clicking on the link under "Event Title"

Shipping Cortisol Samples

European Clinical centers will send bulk shipments of salivary cortisol samples to the Cortisol laboratory for the first 100 children from their site. For these 100 children at each site all three annual Cortisol samples should be sent to the lab for analysis – the 3.5 year sample, the 4.5 year sample and the 5.5 year sample. The remaining subjects' samples should be sent to the NIDDK Central Repository for storage. The DCC will monitor the number of samples that have been sent to the Cortisol laboratory and will contact the Clinical Centers when it is time to start shipping samples to the Repository.

Since US sites started the Cortisol sample collections later than the European sites did, the US sites should follow the guidelines listed below for shipping Cortisol samples:

- 42 month Cortisol Samples – all US sites should ship **ALL** subjects' 42 month samples to the Cortisol Lab. The Psychosocial committee would like at least 400 42 month samples shipped from all US sites combined – the DCC will monitor this number and will notify each site when 42 month samples should start being shipped to the Repository instead of the lab.

- 54 month and 5 year 6 month Cortisol Samples - The Psychosocial committee only wants these samples shipped to the lab if the subject's previous samples have been shipped to the lab (a 54 month sample should only be shipped to the lab if the subject's 42 month sample has been shipped to the lab; a subject's 5 year 6 month sample should only be shipped to the lab if the subject's 42 month sample and 54 month sample have been shipped to the lab), otherwise the committee wants the sample shipped to the Repository. Each month US sites should go to their Clinical Center's reports section on the TEDDY website and review report "III.25 Subjects Whose 54 Month and 5 Year 6 Month Cortisol Samples Should be Shipped to Cortisol Lab" (it will be updated at the end of each month). This report lists all of the subjects whose 54 month and 5 year 6 month samples should be shipped to the lab. If a subject is not listed on the report then the subject's 54 month or 5 year 6 month sample should NOT be shipped to the lab and should instead be shipped to the Repository

Entering information into the "Sample Shipment System" for Cortisol Samples being shipped to the Cortisol Laboratory

1. Logon to the TEDDY website, http://teddy.epi.usf.edu/
2. Go to the "Sample Shipment System" located on the left navigational toolbar under "Data Management".

3. Enter the date of shipment.
4. If you have user access to more than one shipment origin, you will need to choose which destination the samples you are shipping are being shipped from. If you only have user access to one shipment origin, the 'Origin' drop-down menu will be defaulted to that location and you do not need to do anything.
5. Choose the "Cortisol Lab" destination option under "Select where samples will be shipped to".
6. Enter the freezer box number(s) (numbers separated by commas) that you are going to be shipping that day and click "Search".
7. The Local Code, Subject ID, Clinical Center, Test Name, Vial Barcode Number, Visit Location Code, Date Draw, Box/Pouch Number, Space Number, Sample Volume, Site Number (this will only appear for samples being shipped to the Repository) and "Delete From Shipment" option will appear for all the samples that are located in the box(es).
8. Enter the tracking number and courier service for that shipment and any comments you would like to notify the lab about.
9. Click on "Print and Email Shipping List". A dialog box will open that asks "Are you sure you want to print and email the shipment list?" Press 'OK' if you do and 'Cancel' if you don't.
10. Once 'OK' has been clicked an Excel file will be created that will contain information pertaining to each sample (Vial Barcode Number, Subject ID, etc).
11. Save this file for your records; an email containing this file will automatically be sent to the DCC and to the Cortisol Lab.
12. Print out a copy of this list to be shipped with the samples.
13. Repeat this process as necessary until all the boxes you will be sending that day have been entered.

Packing and Shipping Instructions from European or US Sites to Cortisol Laboratory:

1. Place the freezer box along with an absorbent strip inside the inner leak proof poly (plastic) bag. Seal the bag.
2. Place the plastic bag inside the long envelope. Place the box inside the far end of the long pocket of the envelope. Crease the envelope near the middle, fold the envelope over, and place the end of the envelope containing the box inside the short pocket on the opposite side of the envelope. Push the box firmly into the short end of the envelope.
3. Put a layer of dry ice in the bottom of the box. Place the envelopes containing boxes on the dry ice.
4. Fill the remainder of the space in the shipper with dry ice.
5. Put the foam insert, or lid, on top of the dry ice in the opening. Place a copy of the manifest shipping form inside a zip-lock bag, and set it on top of the foam insert under the lid flaps.
6. Close and tape the cardboard box.

7. Attach all labels to the same side of the box:
    a. Stick the dry ice label on the side of the box in the upper right corner. Enter the weight of dry ice on the label.
    b. Place the "UN3373 Diagnostic Specimens" label on the top, center, to the left of the dry ice label.
8. Use the preprinted World House Air Way Bill (HAWB) to ship the samples to the Cortisol Laboratory at the following address:

Division of Clinical Chemistry
Ing-Marie Lundgren Linkoping University Hospital
House 448 floor 11
SE58185 Linkoping, Sweden
Ing-Marie.Lundgren@regionostergotland.se
Phone: +46-101033254

Note: Some TEDDY European sites may choose to use TNT Courier services instead of World Courier services to ship the Salivary Cortisol samples to Linköping University Hospital.

9. Complete the sections of the HAWB that have not been pre-printed
10. Affix the HAWB to the exterior of the shipper. This form is an internal tracking form used by World to identify your shipment from pick-up to delivery. When inquiring about your shipment, reference the waybill number in the top right hand corner. World Courier will provide these forms to you with shipper and consignee information pre-printed.
11. World will send you an example Customs Invoice. Copy this invoice to your letterhead, fill in information for the Date, Shipper, Consignee, and estimate the amount of sample contained in the shipment (in mL) and sign.
12. Affix the Customs Invoice to the shipper exterior.
13. Along with the documents listed above, also give the signed Declaration Statement to the World Courier person picking up the shipment.
14. Call World Courier Services to arrange for pick-up:
    - Finland: 9 8700 3300
    - Germany: 89 9698 9290
    - Sweden: 8 59441 480
    - United States: 1-800-221-6600

You will need to provide the following information to the World Courier Representative:

- DCC Account Number: 10848
- Time of Pick-up
- Specification of types of samples being sent
- Number and type of boxes being shipped
- Special Instructions: Diagnostic shipment.

Entering information into the "Sample Shipment System" for Cortisol Samples being shipped to the Repository

1. Logon to the TEDDY website, http://teddy.epi.usf.edu/
2. Go to the "Sample Shipment System" located on the left navigational toolbar under "Data Management".
3. Enter the date of shipment.
4. If you have user access to more than one shipment origin, you will need to choose which destination the samples you are shipping are being shipped from. If you only have user access to one shipment origin, the 'Origin' drop-down menu will be defaulted to that location and you do not need to do anything.
5. Choose the "Repository" destination option under "Select where samples will be shipped to".
6. Enter the freezer box number(s) (numbers separated by commas) that you are going to be shipping that day and click "Search".
7. The Local Code, Subject ID, Clinical Center, Test Name, Vial Barcode Number, Visit Location Code, Date Draw, Box/Pouch Number, Space Number, Sample Volume, Site Number (this will only appear for samples being shipped to the Repository) and "Delete From Shipment" option will appear for all the samples that are located in the box(es).
8. Enter the tracking number and courier service for that shipment and any comments you would like to notify the lab about.
9. Click on "Print and Email Shipping List". A dialog box will open that asks "Are you sure you want to print and email the shipment list?" Press 'OK' if you do and 'Cancel' if you don't.
10. Once 'OK' has been clicked an Excel file will be created that will contain information pertaining to each sample (Vial Barcode Number, Subject ID, etc).
11. Save this file for your records; an email containing this file will automatically be sent to the DCC and to the Repository.
12. Print out a copy of this list to be shipped with the samples.
13. Repeat this process as necessary until all the boxes you will be sending that day have been entered.

Packing and Shipping Instructions from European Sites to Repository:

1. Please plan for the arrival dates of your shipments - the Repository is closed for business on weekends.
2. Place the freezer box along with an absorbent strip inside the inner leak proof poly (plastic) bag. Seal the bag.
3. Place the plastic bag inside the long envelope. Place the box inside the far end of the long pocket of the envelope. Crease the envelope near the middle, fold the envelope over, and place the end of the envelope containing the box inside the short pocket on the opposite side of the envelope. Push the box firmly into the short end of the envelope.

4. Put a layer of dry ice in the bottom of the box. Place the envelopes containing boxes on the dry ice.
5. Fill the remainder of the space in the shipper with dry ice.
6. Put the foam insert, or lid, on top of the dry ice in the opening. Place a copy of the manifest shipping form inside a zip-lock bag, and set it on top of the foam insert under the lid flaps.
7. Close and tape the cardboard box.
8. Attach all labels to the same side of the box:
   a. Stick the dry ice label on the side of the box in the upper right corner. Enter the weight of dry ice on the label.
   b. Place the "UN3373 Diagnostic Specimens" label on the top, center, to the left of the dry ice label.
   c. Stick the small address label below the "Up" arrows that reads:

      Chris Deigan
      Disease Prevention
      Fisher BioServices
      20301 Century Blvd.
      Building 6, Suite 400
      Germantown MD 20874
      USA

9. Use the preprinted World House Air Way Bill (HAWB) to ship the samples to the NIDDK Biosample Repository at Fisher Bioservices.
10. Complete the sections of the HAWB that have not been pre-printed
11. Affix the HAWB to the exterior of the shipper. This form is an internal tracking form used by World to identify your shipment from pick-up to delivery. When inquiring about your shipment, reference the waybill number in the top right hand corner. World Courier will provide these forms to you with shipper and consignee information pre-printed.
12. World will send you an example Customs Invoice. Copy this invoice to your letterhead, fill in information for the Date, Shipper, Consignee, and estimate the amount of sample contained in the shipment (in mL) and sign.
13. Affix the Customs Invoice to the shipper exterior.
14. Along with the documents listed above, also give the signed Declaration Statement to the World Courier person picking up the shipment.
15. Call World Courier Services to arrange for pick-up:
    - Finland: 9 8700 3300
    - Germany: 89 9698 9290
    - Sweden: 8 59441 480

    You will need to provide the following information to the World Courier Representative:
    - DCC Account Number: 10848
    - Time of Pick-up
    - Specification of types of samples being sent
    - Number and type of boxes being shipped

- Special Instructions: Diagnostic shipment.

16. Notify the repository by email (BIO-NIDDKRepository@FisherSci.com) of an incoming shipment on the day the package is picked up by World Courier. Provide the tracking number, so the repository may track the shipment if it is delayed.

Packing and Shipping Instructions from US Sites to Repository:

1. Please do not ship packages on Friday. The repository is closed for business on weekends.
2. Place the freezer box along with an absorbent strip inside the inner leak proof poly (plastic) bag. Seal the bag.
3. Place the plastic bag inside the long envelope. Place the box inside the far end of the long pocket of the envelope. Crease the envelope near the middle, fold the envelope over, and place the end of the envelope containing the box inside the short pocket on the opposite side of the envelope. Push the box firmly into the short end of the envelope.
4. Place the envelopes in the cardboard inner box, tape the box shut and place it in the middle of the cooler in the shipper. If there is only one vial box in the shipment, fill the rest of the space inside the cardboard inner box with packing material (e.g. bubble wrap or newspaper) to prevent movement during shipment.
5. Fill the remainder of the space between the cardboard box and the inner walls of the cooler with dry ice.
6. Put the lid on the cooler and place the excel printout (containing the sample information) on top of the cooler. Place the "empty packaging cover" (if included – this will be one piece of cardboard that is attached to the outside of the box) on top of the list.
7. Close and tape the outer cardboard box.
8. Place a checkmark in the block on the outer cardboard box next to "BIOLOGICAL SUBSTANCE, CATEGORY B". Do not cover this marking with labels.
9. Affix a label with your name and return address to the side of the box in the "Shipper" block.
10. Affix the repository address label to the side of the box in the "Consignee" block that reads:

Chris Deigan
Disease Prevention
Fisher BioServices
20301 Century Blvd.
Building 6, Suite 400
Germantown MD 20874

11. Affix the dry ice label below the repository address label. Enter the weight of dry ice on the label in kilograms.

12. Affix the "UN3373 BIOLOGICAL SUBSTANCE, CATEGORY B" label to the right of the dry ice label.
13. Use the pre-printed FedEx US air bill to ship the samples to the NIDDK Biosample Repository at Fisher Bioservices.
    a. In Section 1, enter the date, your name, return address and phone number. Leave "Sender's FedEx Account Number" blank
    b. Complete Section 6, Special Handling:
        i. Under "Does this shipment contain dangerous goods?" check "Yes, Shippers Declaration not required".
        ii. Check the "Dry Ice" block and enter "1" and the weight of dry ice in kg.
    c. Under Section 7, Payment:
        i. Enter "1" under "Total Packages".
        ii. Enter the total weight of the package under "Total Weight".
    d. Follow the peel and stick instructions on the back of the air bill (no document holder required).
    e. Attach the air bill to the side of the box adjacent to the labeled sie.
14. Call FedEx at 1.800.Go.FedEx® (800.463.3339) **or** go to http://www.fedex.com/us/ to schedule a pick-up
15. Notify the repository of the incoming shipment and tracking number via email (BIO-NIDDKRepository@FisherSci.com) or fax (301-515-4049) on the day the package is picked up by FedEx.

13.19. Nasal Swab Samples

Beginning at 9 months of age a minimally invasive nasal swab sample will be collected from each TEDDY subject and will continue to be collected at each visit thereafter. The nasal swabs will be collected for the purpose of detection of respiratory infections that may trigger development of islet autoimmunity or progression to T1D. The aim is to cover respiratory viruses and other agents which are difficult to detect from stool or plasma samples. Samples will be collected using commercially available swabs designed for taking nasal swabs from young children (Pediatric Flocked Swabs from Copan Diagnostics Inc). Samples will be taken by the study nurse from one nostril of the child using a minimally invasive method (no deeper than 2 cm inside the nostril in children less than 2 years of age and approximately 3 cm inside the nostril of older children). The sample will be eluted in 1 ml of special Universal Transport Medium in a bar-coded tube (Copan Diagnostics Inc.) and frozen in this tube at -70ºC as soon as possible after the sample has been collected (please see sample collection diagram on next page). Beginning in January 2021 the Pediatric Flocked Swabs were no longer available due to supply shortages from the COVID-19 pandemic. TEDDY began using Copan product # 307C: "3 ml of UTM RT medium in 16X100 mm screw-cap tube with internal shaped conical bottom, one minitip size applicator with flocked nylon fiber tip with breaking point" as well as Copan product # 305C: "3 ml UTM RT medium in 16X100 mm screw-cap tube with internal shaped conical bottom, one flexible minitip size applicator with

flocked nylon fiber tip with breaking point". These tubes could not be etched, so vial barcode labels were used instead.

Frozen samples will be shipped from clinical centers to the NIDDK repository along with plasma samples. Boxes containing nasal swab samples will be stored and shipped in separate plastic bags to ensure that they will not contaminate serum samples.

Since this is a minimally invasive nasal swab there should be little to no discomfort for the child. The swab may tickle and slightly irritate the nose but there should be no pain associated with the procedure.

Equipment

- Copan mini UTM tube (1 ml fill)
- Ped-mid turbinate flocked swab
- Beginning in January 2021 product # 307C: 3 ml of UTM RT medium in 16X100 mm screw-cap tube with internal shaped conical bottom, one minitip size applicator with flocked nylon fiber tip with breaking point or product # 305C: 3 ml UTM RT medium in 16X100 mm screw-cap tube with internal shaped conical bottom, one flexible minitip size applicator with flocked nylon fiber tip with breaking point was used

Preparation

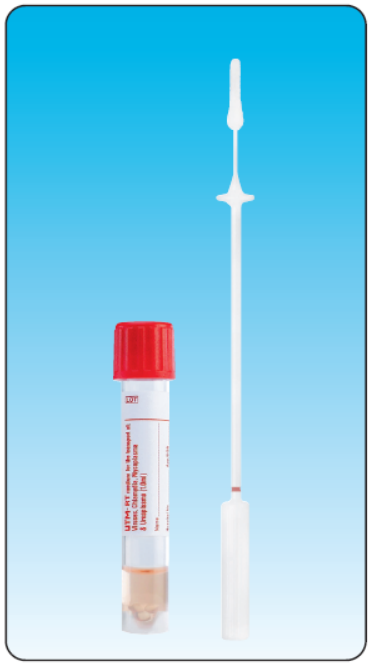
- It is important to communicate with the family and child during the procedure as they may be a little apprehensive.
- The swab and tube should not be removed from the pouch until ready to use.
- If a child has a blocked nose, it may be necessary to encourage the child to blow his/her nose prior to the procedure.

Procedure (see below for visual guide)

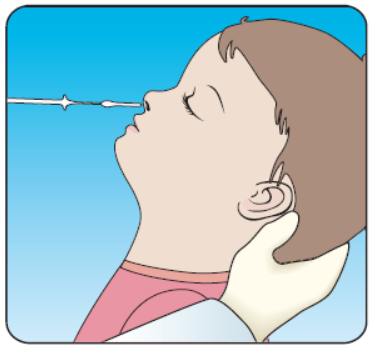
- Explain the procedure to subject and family.
- Wash hands and put on a pair of disposable gloves.
- The child should be placed in the parent's lap. One arm should be placed around the child's waist to help keep him/her sit still.
- Open the peel pouch and have the swab in hand. Do not open the tube of media until after the specimen is obtained. Be careful not to allow the swab to come into contact with anything other than the child's nostril. If the swab is dropped or grabbed by the child, start with a new swab.
- Have the child tilt his/her head back at approximately a 120 degree angle
- Grip the nasal swab below the 3 cm mark but avoid touching the area which will go inside the etched Copan tube.
- Place one hand on the forehead of the child to help stabilize the head for the procedure.
- Insert the swab, parallel to the palate and at the septum, into one nostril (2 cm for children under 2 years and 3 cm for children 2 years and older).

- Sweep gently upwards toward the top of the nostril and rotate the swab 180 degrees so that **the entire surface of the swab comes into contact with the nasal mucous membrane**. Alternatively, you may anchor the swab at the base of the nostril, inside the nostril and against the septum, and rotate the swab 360 degrees ensuring that **the entire surface of the swab comes into contact with the nasal mucous membrane**.
- Remove the top from the etched Copan tube (be careful not to spill the liquid medium).
- Put the swab into the tube and break off end opposite the swab so it fits into the tube.
- Close the cap of the tube.
- The end of the swab shaft may or may not insert into the cap, do not worry about this as long as the tube is securely closed.

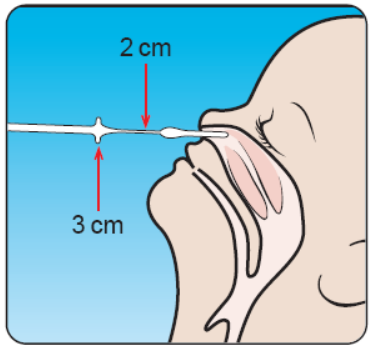
TEDDY STUDY: Collection of Nasal swabs in TEDDY children



TEDDY STUDY components:
- Copan mini UTM tube (1ml fill)
- Ped-mid turbinate flocked swab both in a peel pouch

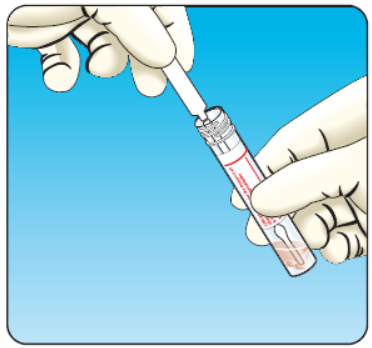


1. Samples taken by the study nurse from one nostril of the child using a minimally invasive method.

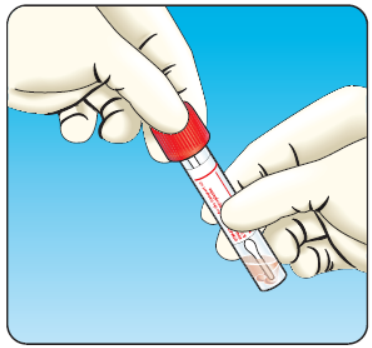


2. Swab should not be inserted any deeper than 2 cm inside the nostril in children less than 2 years of age, and no deeper than 3 cm inside the nostril of older children.

Swab should be rotated gently 180 degrees on the mucosal surface.



3. Open tube and insert swab all of the way into tube. Break swab shaft at break-point (indentation) and dispose of the handle piece.



4. Close the cap of the tube (the end of the swab shaft will insert into the cap).

Freeze immediately at -70° C.

Nasal Swab Sample Collection Form

The SCFs contain constraints that prevent a vial barcode number from being saved more than once. If you try to save a vial barcode number that has already been saved, an error message will appear that explains why the new information cannot be saved. If the vial barcode number that you are trying to save is correct and the same vial barcode number has been entered (and saved) incorrectly for a subject that is within your clinical center, please try to determine the mistake that was made and correct appropriately on the TEDDY website (the Local Code, Subject ID, Visit Name and Test Name associated with the other sample will be provided in the error message) – if you are unable to make the correction yourself contact the DCC at **TEDDY@epi.usf.edu** to make the correction for you. If the sample has already been sent to the Repository or Lab, please contact the Repository or Lab and the DCC with the correct information; once the Repository or Lab verifies that the new information you have given is correct then you should correct this information on the TEDDY website – if you are unable to make the correction yourself contact the DCC at **TEDDY@epi.usf.edu** to make the correction for you. If the vial barcode number was incorrectly entered and saved for a subject that is not within your clinical center, please contact the DCC at **TEDDY@epi.usf.edu**

There are two ways to retrieve the subject's Nasal Sample Collection Form, please see instructions below.

"Sample Collection Form" link

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Sample Collection Form" link under "Data Management" on the left navigational toolbar.
3. Enter both the Subject ID and Local Code of the subject.
4. Select the desired visit.
5. Select the desired Sample Collection Form (i.e. Nasal Swab).
6. Subject ID, Local Code, and Clinical Center fields will be prepopulated on the Sample Collection Form.
7. Choose the correct Visit Location Code from the drop down menu - this is the location where the TEDDY visit took place. Drop-down list based upon TEDDY Clinical Center field.
8. Enter the Date of Collection of the nasal swab sample (DD/MMM/YYYY).
9. **If the sample was processed according to standard TEDDY protocol** (i.e. the Long-Distance protocol was not followed):
   a. Mark the "Sample processed according to standard protocol or Standard protocol followed, insufficient volume" and continue to step 10.
   If the sample was processed according to the Long-Distance protocol:
   b. Indicate the date and time that the sample was processed (this is the time the sample was put in the freezer) and continue to step 10 (parent

should indicate the date the sample was drawn andtime the sample was drawn on the provided form).

NOTE: If sample was drawn/collected in a Long-Distance protocol home that is in a different time zone than the TEDDY Clinical Center the time the sample was drawn and the time the sample was processed should be indicated in the time zone of the Clinical Center and this should be noted on the source document received from the parent

10. In the first grid box below the "Use with Remote Protocol Only" box, find the row containing the "Test Name" (i.e. Nasal Swab Sample) of the sample in the vial you would like to scan.
11. Scan the preprinted barcode located on the cryovial containing this particular sample.
12. In the provided space enter the sample volume (mL) contained in the tube (since the swab is being frozen inside of the tube, enter the volume of the Universal Transport Medium).
13. In the provided space enter box number and space number where the sample will be stored.
13. Click the Save button.

"Enter/Edit/View" Link

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject.
4. Under "Search Results", click on the Local Code of the desired subject.
5. Choose the desired Sample Collection Form by clicking on the links under "Event Title" (i.e. Nasal Swab)
6. Subject ID, Local Code, and Clinical Center fields will be prepopulated on the Sample Collection Form.
7. Choose the correct Visit Location Code from the drop down menu - this is the location where the TEDDY visit took place. Drop-down list based upon TEDDY Clinical Center field.
8. Enter the Date of Collection of the nasal swab sample (DD/MMM/YYYY).
9. **If the sample was processed according to standard TEDDY protocol** (i.e. the Long-Distance protocol was not followed):
    a. Mark the "Sample processed according to standard protocol or Standard protocol followed, insufficient volume" and continue to step 10.

If the sample was processed according to the Long-Distance protocol:

    b. Indicate the date and time that the sample was processed (this is the time the sample was put in the freezer) and continue to step 10 (parent should indicate the date the sample was collected andtime the sample was collected on the provided form).

NOTE: If sample was drawn/collected in a Long-Distance protocol home that is in a different time zone than the TEDDY Clinical Center the time the sample was collected and the time the sample was processed should be indicated in the time zone of the Clinical Center and this should be noted on the source document received from the parent

10. In the first grid box below the "Use with Remote Protocol Only" box, find the row containing the "Test Name" (i.e. Nasal Swab Sample) of the sample in the vial you would like to scan.
11. Scan the preprinted barcode located on the cryovial containing this particular sample.
12. In the provided space enter the sample volume (mL) contained in the tube (since the swab is being frozen inside of the tube, enter the volume of the Universal Transport Medium).
13. In the provided space enter box number and space number where the sample will be stored.
14. Click the Save button.

Shipping: Nasal Swab samples shipped to Repository

Entering information into the "Sample Shipment System
Once a month each clinical center will send bulk shipments of nasal swab samples to the NIDDK Repository.

1. Logon to the TEDDY website, http://teddy.epi.usf.edu/
2. Go to the "Sample Shipment System" located on the left navigational toolbar under "Data Management".
3. Enter the date of shipment.
4. If you have user access to more than one shipment origin, you will need to choose which destination the samples you are shipping are being shipped from. If you only have user access to one shipment origin, the 'Origin' drop-down menu will be defaulted to that location and you do not need to do anything
5. Choose the "Repository" destination option under "Select where samples will be shipped to".
6. Enter the box number for each box that you are going to be shipping that day (numbers separated by commas) and click "Search".
7. The Local Code, Subject ID, Clinical Center, Test Name, Vial Barcode Number, Visit Location Code, Date Draw, Box/Pouch Number, Space Number, Sample Volume, Site Number (this will only appear for samples being shipped to the Repository) and "Delete From Shipment" option will be filled in for all the samples that are located in that box.
8. Enter the tracking number and courier service for that shipment and any comments you would like to notify the lab about.

9. Click on "Print and Email Shipping List". A dialog box will open that asks "Are you sure you want to print and email the shipment list?" Press 'OK' if you do and 'Cancel' if you don't.
10. Once 'OK' has been clicked an Excel file will be created that will contain information pertaining to each sample (Vial Barcode Number, Subject ID, etc).
11. Save this file for your records; an email containing this file will automatically be sent to the DCC and to the Repository.
12. Print out a copy of this list to be shipped with the samples.
13. Repeat this process as necessary until all the boxes you will be sending that day have been entered.

Packing and Shipping Instructions for US Sites:

1. Please do not ship packages on Friday. The repository is closed for business on weekends.
2. Place the 3" freezer box (use 49 cell divider insert for nasal swab samples) and a STP-152 absorbent sheet inside a STP-731 leak proof plastic bag. Seal the bag.
   NOTE: During the supply shortage when Copan product # 307C was used 4" freezer boxes with 36 cell divider inserts and larger shippers were used.
3. Place the plastic bag inside a STP-730 Tyvek envelope, and seal the envelope.
4. Place a thin layer of dry ice in the bottom of the E-65 insulated shipping box.
5. Place up to five filled STP-730 envelopes containing specimen boxes on the dry ice.
6. Fill the remaining space inside the E-65 shipper with dry ice. The shipper should be filled so that there is approximately 3 inches of space in the top of the shipper to insert the black foam lid.
7. Insert the black foam lid and push it down into the shipper so that the outer box can be closed.
8. Place the excel printout (containing the sample information) on top of the black foam lid.
9. Close and tape the outer cardboard box.
10. Affix a label with your name and return address to the long side of the box in the upper left corner.
11. Affix the repository address label below the shipper's return address label.
12. Affix the dry ice label to the upper right corner of the box. Enter the weight of dry ice on the label in kilograms.
13. Affix the "UN3373 BIOLOGICAL SUBSTANCE, CATEGORY B" label to the left of the dry ice label.
14. Use the pre-printed Fed Ex air bill to ship specimens to the NIDDK Biosample Repository at Fisher BioServices:
    a. Section 1: Fill in your name, return address, phone number and the date. Leave "Sender's FedEx Account Number" blank.

   b. Section 6, Special Handling: Check "Yes, Shippers Declaration not required". Check the "Dry Ice" block; enter "1" and the weight of dry ice in kilograms.
   c. Section 7: Enter "1" under "Total Packages" and the total weight of the package.
   d. Follow the peel-and-stick instructions on the back of the air bill. Affix the air bill to the box below the other shipping labels.
15. Call Federal Express at 1-800-GO-FEDEX (1-800-463-3339) or go to http://www.fedex.com/us/ to schedule a pickup. Give FedEx the account number on the preprinted FedEx air bill (in Section 7, Payment) and your pickup address. FedEx will dispatch a courier to pick up the package. Please schedule shipments Monday through Wednesday to avoid weekend shipment delays. Do not ship samples on Friday; the repository is closed on weekends.
16. Send a shipment notification via the online sample shipment system to the repository at **BIO-NIDDKRepository@thermofisher.com** (see section above entitled "Entering information into the "Sample Shipment System" on instructions on how to do this). Include the 12-digit FedEx tracking number in the notification.
17. Contact the NIDDK Biosample Repository via email regarding questions about packaging and shipping.

Packing and Shipping Instructions for European Sites:

1. Please plan for the arrival dates of your shipments - the repository is closed for business on weekends.
2. Place the 3" freezer box (use 49 cell divider insert for nasal swab samples) and an absorbent sheet inside a leak proof plastic bag. Seal the bag.
   NOTE: During the supply shortage when Copan product # 307C was used 4" freezer boxes with 36 cell divider inserts and larger shippers were used.
3. Place the plastic bag inside a Tyvek envelope, and seal the envelope.
4. Place a thin layer of dry ice in the bottom of the insulated shipping box.
5. Place the Tyvek envelopes containing specimen boxes on the dry ice.
6. Fill the remaining space in the shipper with dry ice.
7. Place the lid on top of the insulated shipper.
8. Place the excel printout (containing the sample information) inside a zip-lock bag, and set it on top of the insulated lid.
9. Close and tape the outer cardboard box.
10. Attach all labels to the same side of the box:
    a. Affix a label with your name and return address to the side of the box in the upper left corner.
    b. Affix the dry ice label to the side of the box in the upper right corner. Enter the weight of dry ice on the label.
    c. Affix the "UN3373 BIOLOGICAL SUBSTANCE, CATEGORY B" label to the left of the dry ice label.

11. Use the preprinted World Courier air way bill to ship the samples to the NIDDK Biosample Repository at Fisher BioServices.
12. Complete sections of the air way bill that are not pre-printed.
13. Affix the air way bill to the exterior of the shipper. This form is an internal tracking form used by World Courier to identify your shipment from pick-up to delivery. When inquiring about your shipment, reference the way bill number on the top right corner of the air way bill. World Courier will provide this form to you with preprinted shipper and consignee information.
14. World Courier will send you an example Customs Invoice. Copy this invoice to your letterhead, fill in information for the date, shipper and consignee; estimate the amount of sample contained in the shipment (in mL) and sign the invoice.
15. Affix the Customs Invoice to the shipper exterior in the air way bill pouch.
16. In addition to the documents listed above, provide a signed Declaration Statement to the World Courier representative picking up the shipment.
17. Call World Courier Services to arrange for pick-up:
    - Finland: 9 8700 3300
    - Germany: 89 9698 9290
    - Sweden: 8 59441 480

    You will need to provide the following information to the World Courier Representative:
    - DCC Account Number: 10848
    - Time of Pick-up
    - Description of samples to ship
    - Number and type of boxes to ship
    - Special Instructions: UN 3373 Category B Shipment on dry ice
18. Send a shipment notification via the online sample shipment system to the repository at **BIO-NIDDKRepository@thermofisher.com** (see section above entitled "Entering information into the "Sample Shipment System" on instructions on how to do this). Provide the shipment tracking number, so the repository may track the shipment if it is delayed.
19. Contact the NIDDK Biosample Repository via email regarding questions about packaging and shipping.

13.20. Urine Samples

A 6-15 mL sample of urine should be collected directly into a standard clinical sterile specimen cup from all TEDDY subjects beginning at 3 years of age and will continue to be collected every 6 months (if only less than 6 mL of urine is able to be collected, the sample should still be saved and sent to the Repository). The "clean catch" technique is not required (including girls). All TEDDY subjects are eligible as long as the sample can be processed within 24 hours of collection and can be kept refrigerated/chilled until processing; the sample should be frozen as soon as possible after processing, but within 24 hours of collection. The preferred collection location is the TEDDY clinic, with

specimen cup placed immediately on ice or refrigerated. No preservative and no centrifugation are needed at the TEDDY clinic. Urine should be thoroughly mixed and then divided/transferred EQUALLY into three 8-ml screw-cap etched cryovials and frozen at -80°C until shipment to the NIDDK Repository.

If clinic collection is not possible, then the sample may be collected offsite. If collected offsite, the sample should be refrigerated/chilled continuously and must be processed and frozen at the TEDDY clinic within 24 hours of collection.

Guidelines for shipping liquid samples if collected at a satellite site or on the Long-Distance Protocol:
Four layers of packaging are required for liquid clinical samples

1. A primary, watertight inner receptacle.
   Use watertight containers for liquid specimens with a positive closure such as a screw-on, or a snap-on or push-on lid that is taped or parafilmed for an additional seal. If you place multiple fragile primary receptacles in a single secondary receptacle, they must be individually wrapped or separated to prevent contact between them.
2. Absorbent material
   Place absorbent material between the primary and secondary receptacles, using enough material to absorb the entire contents of all primary receptacles. Examples of absorbent material include cellulose wadding, cotton rolls, super-absorbent packets, and paper towels.
3. Secondary watertight inner receptacle
   Use a watertight sealed plastic bag, plastic canister, or screw-cap can.
4. Sturdy outer packaging
   Use rigid outer packaging made of corrugated fiberboard, styrofoam, wood, metal, or plastic, appropriately sized for the contents. Do not use envelopes without inner packaging, chipboard or paperboard boxes for shipping liquid samples.

No preservative and no centrifugation are needed at the TEDDY clinic. Urine should be thoroughly mixed and then divided/transferred EQUALLY into three 8-ml screw-cap etched cryovials and frozen at -80°C until shipment to the NIDDK Repository.

Urine Sample Collection Form

The SCFs contain constraints that prevent a vial barcode number from being saved more than once. If you try to save a vial barcode number that has already been saved, an error message will appear that explains why the new information cannot be saved. If the vial barcode number that you are trying to save is correct and the same vial barcode number has been entered (and saved) incorrectly for a subject that is within your clinical center, please try to determine the mistake that was made and correct appropriately on the TEDDY website (the Local Code, Subject ID, Visit Name and Test Name associated with the other sample will be provided in the error message) – if you are unable to make the correction yourself contact the DCC at

TEDDY@epi.usf.edu to make the correction for you. If the sample has already been sent to the Repository or Lab, please contact the Repository or Lab and the DCC with the correct information; once the Repository or Lab verifies that the new information you have given is correct then you should correct this information on the TEDDY website – if you are unable to make the correction yourself contact the DCC at **TEDDY@epi.usf.edu** to make the correction for you. If the vial barcode number was incorrectly entered and saved for a subject that is not within your clinical center, please contact the DCC at **TEDDY@epi.usf.edu**

There are two ways to retrieve the subject's Urine Sample Collection Form, please see instructions below.

"Sample Collection Form" link

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Sample Collection Form" link under "Data Management" on the left navigational toolbar.
3. Enter both the Subject ID and Local Code of the subject.
4. Select the desired visit.
5. Select the desired Sample Collection Form (i.e. urine).
6. Subject ID, Local Code, and Clinical Center fields will be prepopulated on the Sample Collection Form.
7. Choose the correct Visit Location Code from the drop down menu - this is the location where the TEDDY visit took place. Drop-down list based upon TEDDY Clinical Center field.
8. Enter the Date of Collection (DD/MMM/YYYY) and time of collection of the urine sample.
9. **If the sample was processed according to standard TEDDY protocol** (i.e. the Long-Distance protocol was not followed):
   a. Mark the "Sample processed according to standard protocol or Standard protocol followed, insufficient volume" and continue to step 10.

   If the sample was processed according to the Long-Distance protocol:
   b. Indicate the date and time that the sample was processed (this is the time the sample was put in the freezer) and continue to step 10 (parent should indicate the date the sample was collected and time the sample was collected on the provided form).

   NOTE: If sample was drawn/collected in a Long-Distance protocol home that is in a different time zone than the TEDDY Clinical Center the time the sample was collected and the time the sample was processed should be indicated in the time zone of the Clinical Center and this should be noted on the source document received from the parent.

10. Indicate the number of hours the sample was at ambient temperature in the provided space.
11. Find the row containing the "Test Name" (i.e. Urine Sample #1, Urine Sample #2, Urine Sample #3) of the sample in the vial you would like to scan. Sites

should aliquot all urine samples equally amongst the 3 cryovials, so very rarely should the site need to indicate "insufficient volume". For those very rare occasions when an insufficient volume amount was obtained, and there is not enough for that particular Test Name, check the "Insufficient Blood Volume" Box in that row, repeat this step as necessary then continue to step 17; if there is a sufficient amount of urine go to step 12.

12. Place cursor in the "Vial Barcode Number" box in this row.
13. Scan the preprinted barcode located on the cryovial containing this particular sample.
14. In the provided space enter the sample volume (mL) contained in the cryovial.
15. In the provided space enter box number and space number where the sample will be stored.
16. Place the cryovial in the exact freezer box and space number that you entered on the SCF for that particular sample.
17. Repeat steps 11-16 as necessary.
18. When all samples for this specific SCF have been entered, click the "Save Form" button at the top of this form.

"Enter/Edit/View" Link

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject.
4. Under "Search Results", click on the Local Code of the desired subject.
5. Choose the desired Sample Collection Form by clicking on the links under "Event Title" (i.e. Urine Sample)
6. Subject ID, Local Code, and Clinical Center fields will be prepopulated on the Sample Collection Form.
7. Choose the correct Visit Location Code from the drop down menu - this is the location where the TEDDY visit took place. Drop-down list based upon TEDDY Clinical Center field.
8. Enter the Date of Collection (DD/MMM/YYYY) and time of collection of the urine sample.
9. **If the sample was processed according to standard TEDDY protocol** (i.e. the Long-Distance protocol was not followed):
   a. Mark the "Sample processed according to standard protocol or Standard protocol followed, insufficient volume" and continue to step 10.

   If the sample was processed according to the Long-Distance protocol:
   b. Indicate the date and time that the sample was processed (this is the time the sample was put in the freezer) and continue to step 10 (parent should indicate the date the sample was collected and time the sample was collected on the provided form).

NOTE: If sample was drawn/collected in a Long-Distance protocol home that is in a different time zone than the TEDDY Clinical Center the time the sample was collected and the time the sample was

processed should be indicated in the time zone of the Clinical Center and this should be noted on the source document received from the parent.

10. Indicate the number of hours the sample was at ambient temperature in the provided space.
11. Find the row containing the "Test Name" (i.e. Urine Sample #1, Urine Sample #2, Urine Sample #3) of the sample in the vial you would like to scan. Sites should aliquot all urine samples equally amongst the 3 cryovials, so very rarely should the site need to indicate "insufficient volume". For those very rare occasions when an insufficient volume amount was obtained, and there is not enough for that particular Test Name, check the "Insufficient Blood Volume" Box in that row, repeat this step as necessary then continue to step 17; if there is a sufficient amount of urine go to step 12.
12. Place cursor in the "Vial Barcode Number" box in this row.
13. Scan the preprinted barcode located on the cryovial containing this particular sample.
14. In the provided space enter the sample volume (mL) contained in the cryovial.
15. In the provided space enter box number and space number where the sample will be stored.
16. Place the cryovial in the exact freezer box and space number that you entered on the SCF for that particular sample.
17. Repeat steps 11-16 as necessary.
18. When all samples for this specific SCF have been entered, click the "Save Form" button at the top of this form.

Storage

Store urine samples at -80°C. Send samples to the repository in bulk shipments on dry ice once a month.

Shipping: Urine samples shipped to Repository

Entering information into the "Sample Shipment System"

Once a month each clinical center will send bulk shipments of urine samples to the NIDDK Repository.

1. Logon to the TEDDY website, http://teddy.epi.usf.edu/
2. Go to the "Sample Shipment System" located on the left navigational toolbar under "Data Management".
3. Enter the date of shipment.
4. If you have user access to more than one shipment origin, you will need to choose which destination the samples you are shipping are being shipped from. If you only have user access to one shipment origin, the 'Origin' drop-down menu will be defaulted to that location and you do not need to do anything.
5. Choose the "Repository" destination option under "Select where samples will be shipped to".

6. Enter the box number for each box that you are going to be shipping (numbers separated by commas) and click "Search".
7. The Local Code, Subject ID, Clinical Center, Test Name, Vial Barcode Number, Visit Location Code, Date Draw, Box/Pouch Number, Space Number, Sample Volume, Site Number (this will only appear for samples being shipped to the Repository) and "Delete From Shipment" option will be filled in for all the samples that are located in that box.
8. Enter the tracking number and courier service for that shipment and any comments you would like to notify the lab about.
9. Click on "Print and Email Shipping List". A dialog box will open that asks "Are you sure you want to print and email the shipment list?" Press 'OK' if you do and 'Cancel' if you don't.
10. Once 'OK' has been clicked an Excel file will be created that will contain information pertaining to each sample (Vial Barcode Number, Subject ID, etc).
11. Save this file for your records; an email containing this file will automatically be sent to the DCC and to the Repository.
12. Print out a copy of this list to be shipped with the samples.
13. Repeat this process as necessary until all the boxes you will be sending that day have been entered.

Packing and Shipping Instructions for US Sites:

1. Please do not ship packages on Friday. The repository is closed for business on weekends.
2. Place the 3" freezer box along with a STP-152 absorbent strip inside a STP-731 inner leak proof poly (plastic) bag. Seal the bag.
3. Place the poly bag inside a STP-730 envelope, fold over and tuck the STP-730 into pocket.
4. Place up to three filled STP-730 envelopes in the cardboard inner box, tape the box shut and place it in the middle of the cooler in the STP-309 shipper. If there are only one or two vial boxes in the shipment, fill the rest of the space inside the cardboard inner box with packing material (e.g. bubble wrap or newspaper) to prevent movement during shipment.
5. Fill the remainder of the space between the cardboard box and the inner walls of the cooler with dry ice.
6. Put the lid on the cooler and place the excel printout (containing the sample information) on top of the cooler. Place the "empty packaging cover" (if included – this will be one piece of cardboard that is attached to the outside of the box) on top of the list.
7. Close and tape the outer cardboard box.
8. Attach labels to side of box with "Biological Products Diagnostic Specimens" statement:
    a. Stick the Class 9 dry ice label in the upper left corner (of the SIDE of the box). Enter the weight of dry ice as 8 kg.

b. Stick a separate address label in the lower left corner, under the dry ice label, that reads:

Chris Deigan
Disease Prevention
Fisher BioServices
20301 Century Blvd.
Building 6, Suite 400
Germantown MD 20874
USA

c. Stick the "UN3373 Diagnostic Specimens" label to the right of the dry ice label.

9. Use the pre-printed FedEx US air bill to ship the samples to the Fisher/NIDDK Biosample Repository.
    a. In Section 1, enter the date, your name, return address and phone number. Leave "Sender's FedEx Account Number" blank
    b. Complete Section 6, Special Handling:
        a. Under "Does this shipment contain dangerous goods?" check "Yes, Shippers Declaration not required".
        b. Check the "Dry Ice" block and enter "1" x "8" kg.
    c. Under Section 7, Payment:
        a. Enter "1" under "Total Packages".
        b. Enter "24 lbs" under "Total Weight" (this is the total weight if the shipper contains 3 freezer boxes with 81 samples in each).
        c. Follow the peel and stick instructions on the back of the air bill (no document holder required).
        d. Attach the air bill to the lower right corner of the side of the
        e. box.
10. Call FedEx at 1.800.Go.FedEx® (800.463.3339) **or** go http://www.fedex.com/us/ to schedule a pick-up
11. Notify the repository of the incoming shipment and tracking number via email (BIO-NIDDKRepository@FisherSci.com) or fax (301-515-4049) on the day the package is picked up by FedEx.

Packing and Shipping Instructions for European Sites:

1. Please plan for the arrival dates of your shipments -.the repository is closed for business on weekends.
2. Place the 3" freezer box along with an absorbent strip inside the inner leak proof poly (plastic) bag. Seal the bag.
3. Place the plastic bag inside the long Tyvek envelope. Place the box inside the far end of the long pocket of the envelope. Crease the envelope near the middle, fold the envelope over, and place the end of the envelope containing the box inside the short pocket on the opposite side of the envelope. Push the box firmly into the short end of the envelope.

4. Put a layer of dry ice in the bottom of the box. Place up to 5 Tyvek envelopes containing boxes on the dry ice.
5. Fill the remainder of the space in the shipper with dry ice up to about four inches from the top.
6. Put the foam insert on top of the dry ice in the opening. Place a copy of the manifest shipping form inside a zip-lock bag, and set it on top of the foam insert under the lid flaps.
7. Close and tape the cardboard box.
8. Attach all labels to the same side of the box:
    a. Stick the dry ice label on the side of the box in the upper right corner. Enter the weight of dry ice as 14 kg.
    b. Place the "UN3373 Diagnostic Specimens" label on the top, center, to the left of the dry ice label.
    c. Stick the small address label below the "Up" arrows that reads:

Chris Deigan
Disease Prevention
Fisher BioServices
20301 Century Blvd.
Building 6, Suite 400
Germantown MD 20874
USA

9. Use the preprinted World House Air Way Bill (HAWB) to ship the samples to the Fisher/NIDDK Biosample Repository.
    a. Complete the sections of the HAWB that have not been pre-printed
    b. Affix the HAWB to the exterior of the shipper. This form is an internal tracking form used by World to identify your shipment from pick-up to delivery. When inquiring about your shipment, reference the waybill number in the top right hand corner. World Courier will provide these forms to you with shipper and consignee information pre-printed.
    c. World will send you an example Customs Invoice, you need to copy this invoice to your letterhead, fill in information for the Date, Shipper, Consignee, and estimate the amount of sample contained in the shipment (in mL) and sign.
    d. Affix the Customs Invoice to the shipper exterior
    e. Along with the documents listed above, also give the signed Declaration Statement to the World Courier person picking up the shipment.
10. Call World Courier Services to arrange for pick-up:
    - Finland: 9 8700 3300
    - Germany: 89 9698 9290
    - Sweden: 8 59441 480

    You will need to provide the following information to the World Courier Representative:
    - DCC Account Number: 10848
    - Time of Pick-up

- Specification of types of samples being sent
- Number and type of boxes being shipped
- Special Instructions: Diagnostic shipment.

11. Notify the repository by email (BIO-NIDDKRepository@FisherSci.com) of an incoming shipment on the day the package is picked up by World. Provide the tracking number, so the repository may track the shipment if it is delayed.

13.21. Primary Tooth Samples

The intent is to collect at least one tooth from each child when they naturally fall out. Parents will be asked to save the tooth, write down the date the tooth fell out (DD/MMM/YYYY) and bring it to their next TEDDY clinic visit. Since most TEDDY visits are every six months, it is acceptable for the parents to keep the tooth for six or more months before bringing it to the TEDDY clinic as long as they write down the date the tooth fell out (DD/MMM/YYYY). The parent should try not to wash the tooth off, but if they do it is still acceptable to the study. The parent should NOT store the tooth in hydrogen peroxide or any other liquid, as it causes problems at analysis. TEDDY will accept teeth that have been capped and/or filled. The site will store the tooth in a 2 ml etched vial and record the date it fell out. The site should not wash or do anything to the tooth.

Planned analyses of the teeth provide a record of environmental exposures throughout the child's life since teeth form daily growth rings. The technology to measure these exposures which extend to both prenatal and post-natal periods include metal exposures as well as bone constituents. This technology is developing and may provide measures of other exposures that might be informative to TEDDY.

It is clear that this is a convenience sample in that there is no expectation that teeth will be collected on every child, or that the teeth which are collected will come from children of the same age. The availability of the teeth will determine which analyses are feasible. At a minimum, the available teeth can verify the parent reported record of exposure and can be used to correlate with measures obtained from serum and/or plasma. Should more than one tooth be available from a TEDDY child, the study will accept all available which would provide more material to analyze.

Primary Tooth Sample Collection Form

1) Logon to the TEDDY website http://teddy.epi.usf.edu/
2) Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3) Search for the desired subject.
4) Under "Search Results", click on the Local Code of the desired subject.
5) Choose "Primary Tooth Sample Collection Form" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.

6) Click 'Select Form' button that is below dropdown menu.
7) Choose the correct Visit Location Code from the drop down menu - this is the location where the TEDDY visit took place. Drop-down list based upon TEDDY Clinical Center field.
8) Enter the Date Tooth fell out (DD/MMM/YYYY)
9) Find the row containing the "Test Name" (i.e. Primary Tooth Sample) of the sample in the vial you would like to scan.
10) Place cursor in the "Vial Barcode Number" box in this row.
11) Scan the preprinted barcode located on the cryovial containing this sample.
12) In the provided space enter box number and space number where the sample will be stored.
13) Place the cryovial in the exact freezer box and space number that you entered on the SCF for that particular sample.
14) Click the "Save Form" button at the top of this form and close the form.

Once the Participant's Details Page has been refreshed, you will see "Primary Tooth Sample Collection Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1) Click on the form link under 'Completed Additional Study Forms'
2) A new window will open which will have links to all of the "Primary Tooth Sample Collection Forms" that have been saved for this subject.
3) Click on an 'event date' link to open up a specific form for this subject.

Storage

Store teeth samples at room temperature out of direct sunlight or any heat source. Do not freeze as teeth become brittle when frozen. Send samples to the repository in bulk shipments at room temperature (teeth samples must be shipped separate from other TEDDY samples as they cannot be shipped on dry ice).

In instances where a large tooth (e.g. molar) is collected in which the size of the tooth prevents the use of the 2 ml cryovial, it is acceptable to use the 8 ml tube. The 8 ml tube should be placed in a separate box by itself within the same shipment and the shipping log should be amended to alert the Repository of this situation.

Shipping: Teeth samples shipped to Repository

Entering information into the "Sample Shipment System"

Each clinical center will send bulk shipments of teeth samples to the NIDDK Repository.

1) Logon to the TEDDY website, http://teddy.epi.usf.edu/
2) Go to the "Sample Shipment System" located on the left navigational toolbar under "Data Management".
3) Enter the date of shipment.

4) If you have user access to more than one shipment origin, you will need to choose which origin the samples you are shipping are being shipped from. If you only have user access to one shipment origin, the 'Origin' drop-down menu will be defaulted to that location and you do not need to do anything.
5) Choose the "Repository" destination option under "Select where samples will be shipped to".
6) Enter the box number for each box that you are going to be shipping (numbers separated by commas) and click "Search".
7) The Local Code, Subject ID, Clinical Center, Test Name, Vial Barcode Number, Visit Location Code, Date tooth fell out, Box Number, Space Number, Sample Volume, Site Number (this will only appear for samples being shipped to the Repository) and "Delete From Shipment" option will be filled in for all the samples that are located in that box.
8) Enter the tracking number and courier service for that shipment and any comments you would like to notify the lab about.
9) Click on "Print and Email Shipping List". A dialog box will open that asks "Are you sure you want to print and email the shipment list?" Press 'OK' if you do and 'Cancel' if you don't.
10) Once 'OK' has been clicked an Excel file will be created that will contain information pertaining to each sample (Vial Barcode Number, Subject ID, etc).
11) Save this file for your records; an email containing this file will automatically be sent to the DCC and to the Repository.
12) Print out a copy of this list to be shipped with the samples.
13) Repeat this process as necessary until all the boxes you will be sending that day have been entered.

Packing and Shipping Instructions for US Sites:

1) Please do not ship packages on Friday. The repository is closed for business on weekends.
2) Place the freezer box inside a STP-731 inner leak proof poly (plastic) bag. Seal the bag.
3) Place the poly bag inside a STP-730 envelope, fold over and tuck the STP-730 into pocket.
4) Place up to three filled STP-730 envelopes in the cardboard inner box, tape the box shut and place it in the middle of the cooler in the STP-309 shipper. If there are only one or two vial boxes in the shipment, fill the rest of the space inside the cardboard inner box with packing material (e.g. bubble wrap or newspaper) to prevent movement during shipment.
5) Put the lid on the cooler and place the excel printout (containing the sample information) on top of the cooler. Place the "empty packaging cover" (if included – this will be one piece of cardboard that is attached to the outside of the box) on top of the list.
6) Close and tape the outer cardboard box.
7) Attach label to side of box with "Biological Products Diagnostic Specimens" statement.
    - Stick a separate address label in the lower left corner that reads:

Chris Deigan
Disease Prevention
Fisher BioServices
20301 Century Blvd.
Building 6, Suite 400
Germantown MD 20874
USA

- Stick the "UN3373 Diagnostic Specimens" label to the right

8) Use the pre-printed FedEx US air bill to ship the samples to the Fisher/NIDDK Biosample Repository.
   - In Section 1, enter the date, your name, return address and phone number. Leave "Sender's FedEx Account Number" blank
   - Complete Section 6, Special Handling:
     i. Under "Does this shipment contain dangerous goods?" check "Yes, Shippers Declaration not required".
9) Under Section 7, Payment:
   - Enter "1" under "Total Packages".
   - Enter "Total Weight"
10) Follow the peel and stick instructions on the back of the air bill (no document holder required).
11) Attach the air bill to the lower right corner of the side of the box.
   - Call FedEx at 1.800.Go.FedEx® (800.463.3339) **or** go http://www.fedex.com/us/ to schedule a pick-up
12) Notify the repository of the incoming shipment and tracking number via email (BIO-NIDDKRepository@FisherSci.com) on the day the package is picked up by FedEx.

Packing and Shipping Instructions for European Sites:

1) Please plan for the arrival dates of your shipments -.the repository is closed for business on weekends.
2) Place the freezer box inside a STP-731 inner leak proof poly (plastic) bag. Seal the bag.
3) Place the poly bag inside a STP-730 envelope, fold over and tuck the STP-730 into pocket.
4) Place up to three filled STP-730 envelopes in the cardboard inner box, tape the box shut and place it in the middle of the cooler in the STP-309 shipper. If there are only one or two vial boxes in the shipment, fill the rest of the space inside the cardboard inner box with packing material (e.g. bubble wrap or newspaper) to prevent movement during shipment.
5) Put the lid on the cooler and place the excel printout (containing the sample information) on top of the cooler. Place the "empty packaging cover" (if included – this will be one piece of cardboard that is attached to the outside of the box) on top of the list.
6) Close and tape the outer cardboard box.
7) Attach all labels to the same side of the box:

- Place the "UN3373 Diagnostic Specimens" label on the top, center.
- Stick the small address label below the "Up" arrows that reads:

Chris Deigan
Disease Prevention
Fisher BioServices
20301 Century Blvd.
Building 6, Suite 400
Germantown MD 20874
USA

8) Use the preprinted World House Air Way Bill (HAWB) to ship the samples to the Fisher/NIDDK Biosample Repository.
9) Complete the sections of the HAWB that have not been pre-printed
10) Affix the HAWB to the exterior of the shipper. This form is an internal tracking form used by World to identify your shipment from pick-up to delivery. When inquiring about your shipment, reference the waybill number in the top right hand corner. World Courier will provide these forms to you with shipper and consignee information pre-printed.
11) World will send you an example Customs Invoice, you need to copy this invoice to your letterhead, fill in information for the Date, Shipper, Consignee, and estimate the amount of sample contained in the shipment (in mL) and sign.
12) Affix the Customs Invoice to the shipper exterior.
13) Along with the documents listed above, also give the signed Declaration Statement to the World Courier person picking up the shipment.
14) Call World Courier Services to arrange for pick-up:
    - Finland: 9 8700 3300
    - Germany: 89 9698 9290
    - Sweden: 8 59441 480
15) You will need to provide the following information to the World Courier Representative:
    - DCC Account Number: 10848
    - Time of Pick-up
    - Specification of types of samples being sent
    - Number and type of boxes being shipped
    - Special Instructions: Diagnostic shipment.
16) Notify the repository by email (BIO-NIDDKRepository@FisherSci.com) of an incoming shipment on the day the package is picked up by World. Provide the tracking number, so the repository may track the shipment if it is delayed.

Section 13 - Appendix:

- **A. Physical Examination Form**
- **B. Tap Water Collection Instructions**
  1. **English version**
  2. **German version**
  3. **Swedish version**
  4. **Finnish version**
  5. **Spanish version**
- **C. Pre-visit Toenail Sample Preparation Instructions for Parents**
  1. **English version**
  2. **Swedish version**
  3. **Spanish version**
- **D. Toenail Sample Collection Instructions for Parents**
  1. **English version**
  2. **German version**
  3. **Swedish version**
  4. **Finnish version**
- **E. Salivary Cortisol Sample Collection Instructions for Parents**
  1. **English version**
  2. **German version**
  3. **Swedish version**
  4. **Finnish version**
- **F. Information for Parents on Caffeine Content of Beverages, Foods and Drugs to Avoid Giving to Child Before Salivary Cortisol Sample Collection**
  1. **US products**
  2. **German products**
- **G. Model letter to parent for home finger stick sample**
- **H. Model instructions to parent for home finger stick sample**
- **I. Site Specific Instructions to Parent for Home Finger Stick Sample: Germany**
- **J. Draft of Talking Points on Increased Blood Volume IRB, Staff, and Families (from Georgia Site)**
- **K. Tooth Collection Instructions**
  1. **Washington version**
  2. **German version**
  3. **Colorado version (English and Spanish)**
  4. **Florida version**
  5. **Swedish version**
  6. **Georgia version**
  7. **Finnish version**
- **L. Tooth Fairy Letter**
  1. **Washington version**
  2. **Colorado version**
- **M. Home Glucose Testing Instructions**
  1. **Colorado version**
  2. **Swedish version**
  3. **Finnish version**
  4. **Georgia version**

Appendix A: PHYSICAL EXAMINATION FORM

(Note – section 3C is associated with the Long-Distance Protocol and is to be filled out by remote lab only, not TEDDY clinical center)

39257 *Local Use Only* **SubjectID**

1) Please record the TEDDY child's weight and length/height. The infant should be weighed lying on his/her back without clothes and diaper. Children old enough to stand on a scale should be measured in light clothing. Length is measured on all children up to two years old. It should be measured with the child lying on his/her back from heels (without shoes) to the top of the head. After the child is two years old the standing height should be measured with the child standing, without shoes.

a) Weight: ___.___ kilograms

b) Length/ Height: ___.___ centimeters

○ Weight & Length/Height collected by long-distance protocol
- ○ By healthcare professional
- ○ By parent

If Weight & Length/Height were collected by long-distance protocol indicate the date of measurement below:

__/__/____ (DD/MMM/YYYY - *Example 01/JAN/2004*)

○ Weight & Length/Height collected by non-standard TEDDY protocol
- ○ By healthcare professional
- ○ By parent
- ○ By TEDDY staff member

If Weight & Length/Height were collected by non-standard TEDDY protocol indicate the date of measurement below:

__/__/____ (DD/MMM/YYYY - *Example 01/JAN/2004*)

2) Tanita scale measurements; follow instructions for using machine listed in the TEDDY MOO

a) Tanita scale weight ___.___ kilograms

b) Tanita scale kilograms of body fat ___.___ kilograms
- ☐ Tanita machine not available
- ☐ Parent/child refused

3) Below please record the amount of blood drawn, the draw site, the date and time the sample was drawn and the date it was shipped:

a) Total Amount of Blood Drawn: ___.___ mL

b) Draw Site (mark either Venous or Capillary - mark only 1 site where blood was drawn from):

○ Venous	○ Capillary
○ Left antecubital	○ Left heel
○ Right antecubital	○ Right heel
○ Left hand	○ Finger
○ Right hand	○ Other
○ Other	

Physical Examination Form Page 2 of 3 Form Revision date: 1 May 2017

39257

Local Use Only

SubjectID

*c) Date Sample was Drawn: / / (DD/MMM/YYYY - *Example 01/JAN/2004*)

Time Sample was Drawn: : (Please record time in Universal Time - for example 2 pm would be recorded as 14:00)

Date Sample was Shipped: / / (DD/MMM/YYYY - *Example 01/JAN/2004*)

Estimated Total Blood Volume (within ~1 ml) of whole blood added to all CPT tubes from this draw used for PBMC isolation, prior to processing = . ml

This is the amount of whole blood added from syringe, not the final volume including reagent in the tube. If you drew directly into CPT tube, use a calibrated tube to measure volume of whole blood added.

* **Section 3c to be completed by remote lab only.**

4) Please record if the family was referred to another healthcare specialist:

○ Yes ○ No

a) Date of Referral: / /

b) Reason for Referral:

***If child tests positive for any Autoantibody, a random plasma/blood glucose test will be done at every visit. Please record the blood glucose level and draw site below.

Blood glucose level: mg/dL

or

. mmol/l

Draw Site: ○ Venous Blood ○ Capillary Blood ○ Venous Plasma

5) Has the subject participated in a new research study (other than TEDDY) since his/her last TEDDY visit or is the subject still participating in another study that has been previously indicated on the "Participant in Non-TEDDY Research Form"?

○ Yes ○ No

If yes, please complete a new "Participant in Non-TEDDY Research Form".

Comments:

_____

_____

_____

_____

Physical Examination Form Page 3 of 3 Form Revision date: 1 May 2017

Appendix B1: TAP WATER COLLECTION INSTRUCTIONS - English version

TEDDY Study
Drinking Water Collection Instructions

Supplies

a. Six - 2 ml collection tubes
b. Ziploc bag to hold tubes

Instructions

We would like to get a sample of the water from your house that you give to your baby ***(note to staff: baby should be replaced with "child" for 3 year water sample instructions and beyond)*** most often. This is the water your baby gets in a bottle or is mixed with infant formula, cereal, or juice ***(note to staff: this sentence or parts of this sentence could be deleted from 3 year water sample instructions and beyond)***. This might be tap water, bottled water, distilled water, or water from your refrigerator. Choose the type of water your child gets most often. If you normally boil, distill, or filter the water, follow your normal routine for this sample as well. Please allow boiled water to cool prior to filling the collection tubes.

Please collect the sample the morning of your 9 month visit ***(note to staff: replace with 3 year visit, 5 year visit, etc. as necessary)*** **and bring it with you to the clinic.**

a. Take six collection tubes to your water source and remove the caps. Find the 1.8 line on the collection tubes.
b. If you are collecting water from your tap, adjust the water flow for ease of collection. From other sources, like a refrigerator, it may be necessary to first put the water in a glass or measuring cup and then fill the tubes.
c. Fill each of the 6 tubes to the 1.8 line on the side of the tube. (Please make sure not to fill past the 1.8 line; we will be freezing these samples and if the water is filled past this line there is not enough room for expansion.)
d. Secure caps on the tubes. Place the tubes in the box Ziploc bag provided note the date and water source below and bring to the 9-month clinic visit.
e. Examine the Ziploc bag to make sure that all six tubes are filled to the fill line, their caps are securely fastened, and there is no leakage.

If you have any questions, please call our office at xxxxx and we will be happy to help.
Thank you.

Collection Date: _____

What is the water source?

_____Tap water from city
_____Tap water from well or spring
_____Tap water, unknown source
_____Bottled water
_____Other _____

Mark all that apply

_____Filtered
_____Boiled
_____Distilled

Appendix B2: TAP WATER COLLECTION INSTRUCTIONS - German version

Anleitung zum Sammeln der Wasserproben im 9. Monat

Wir würden gerne eine Wasserprobe aus Ihrem Haushalt sammeln. Es handelt sich dabei um das Wasser, das Sie Ihrem Kind als Getränk (z.B. pur, gemischt mit Saft, als Tee) sowie zur Zubereitung der Säuglingsmilchnahrung oder anderer Nahrung verwenden. Dies kann Leitungswasser, gekauftes, abgefülltes Wasser oder gefiltertes Leitungswasser sein. Wählen Sie das Wasser, das Ihr Kind am häufigsten erhält.

Bitte sammeln Sie die Wasserprobe im 9. Lebensmonat Ihres Kindes.

1) Wenn Sie eine Probe Ihres Leitungswassers aus dem Hahn nehmen, halten Sie einen Behälter nach dem anderen in den Wasserstrahl. Füllen Sie die Behälter bis zur „Fülllinie“ auf. Bitte kaltes Wasser verwenden.

2) Wenn Sie gekauftes, abgefülltes Wasser oder gefiltertes Wasser verwenden, schütten Sie evtl. das Wasser zuvor in ein Glas oder einen Messbecher und füllen Sie anschließend damit die Behälter bis zur „Fülllinie“ auf.

3) Schrauben Sie die Deckel fest auf die Behälter und schicken Sie uns die Wasserproben per DHL Express Service (siehe Hinweise zum Versand) zu.

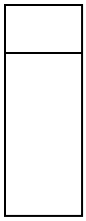
Falls Sie dazu Fragen haben, können Sie uns jederzeit unter der kostenlosen TEDDY-Hotline 0800 – 33 83339 bzw. 0800 – 33 TEDDY erreichen. Wir werden Ihnen dann alle Fragen beantworten.

Danke für Ihre Mithilfe!

Hinweise zum Sammeln der Wasserproben

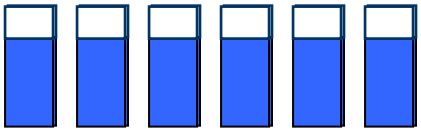
Sie erhalten von uns 6 Plastikbehälter

mit einer Fülllinie bei 1,8 ml.

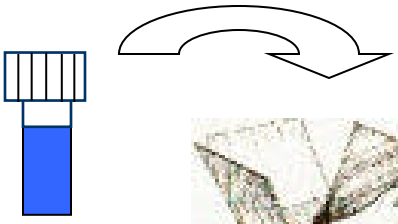


Sammeln Sie das Wasser
(z.B. Leitungswasser oder gekauftes, abgefülltes Waser):

Füllen Sie dazu alle 6 Behälter bis zur Fülllinie mit dem Wasser auf.



Schrauben Sie die Deckel auf die Behälter und



und legen Sie die 6 fest verschraubten Behälter
in die dafür vorgesehene Box:

Rufen Sie beim ***DHL Express Service*** an und bestellen Sie einen Kurier

Tel.: 01805-345 22 55

Appendix B3: TAP WATER COLLECTION INSTRUCTIONS - Swedish version

INSTRUKTION FÖR PROVTAGNING AV DRICKSVATTEN

Vi skulle vilja ha ett prov av det vatten som ni **för det mesta** ger barnet. Det kan vara vattnet barnet får i nappflaskan eller som ni blandar med välling-, juice- eller grötpulver. Beroende på vad ni oftast ger barnet kan det vara vatten direkt från kranen eller från flaska. Vattnet kan vara kokt, destillerat eller filtrerat. Välj alltså det vatten som ni oftast ger till barnet. Om ni kokar vattnet så låt det kallna innan ni fyller det i provrören.

Fyll provrören med vattnet samma morgon som ni ska komma till TEDDY-mottagningen på 9-månadersbesöket .

a. Ta av locket från de 6 provrören. Titta efter ”1.8 linjen” på provrören.

b. Om du ska ta vatten direkt från kranen, se till att vattnet inte rinner för häftigt. Sätt ett provrör i taget i vattenstrålen. Fyll upp till ”1.8 linjen”.

c. Om du tar vatten från en flaska kan du först behöva hälla upp vatten i en liten tillbringare eller något annat kärl med en pip och sedan fylla rören upp till “1.8 linjen”.

d. Fyll alla 6 rören upp till ”1.8 linjen”.

e. Fyll i blanketten som följer med rören i plastpåsen.

f. Lägg alla rören i plastpåsen tillsammans med blanketten och ta med dem till TEDDY-besöket.

g. Kontrollera att alla rören har fyllts till ”1.8 linjen” och att locken sitter på ordentligt, så rören inte läcker.

Om ni undrar över något så ring er TEDDY-sköterska.

(This paper slip is put into the plastic bag together with the collection tubes. The ID's are filled in before the family gets the tubes.)

VATTENPROV

SUBJECT ID_____LOCAL ID_____

Datum då provet togs:_____

Vilken typ av vatten är det? (markera i ringen)

O Kranvatten från kommunen

O Kranvatten från egen brunn

O Kranvatten, men vet inte varifrån det kommer

o Vatten från flaska

O Annat vatten .....

Är vattnet filtrerat? O ja O nej

Är vattnet kokt? O ja O nej

Är vattnet destillerat? O ja O nej

Appendix B4: TAP WATER COLLECTION INSTRUCTIONS - Finnish version

TEDDY-tutkimus
Juomavesinäytteen keräysohjeet

Tarvikkeet:

a. Kuusi 2 ml keräysputkea
b. Suljettava muovipussi putkien säilytykseen

Ohjeet:

Haluaisimme saada näytteen vedestä, jota useimmin annatte lapsellenne. Tätä vettä lapsi saa pullosta tai sekoitettuna äidinmaidonkorvikkeeseen, velliin tai mehuun. Vesi voi olla vesijohtovettä, pullotettua vettä, tislattua vettä tai vettä jääkaapistanne. Valitkaa se vesi, jota lapsenne saa useimmin. Jos normaalisti keitätte, tislaatte tai suodatatte veden, noudattakaa tämän näytteen suhteen tavallista käytäntöänne. Antakaa keitetyn veden jäähtyä ennen kuin täytätte keräysputket.

Kerätkää näyte sinä aamuna, kun tulette 9 kk:n käynnille ja tuokaa se mukananne vastaanotolle.

f. Ottakaa kuusi keräysputkea vesilähteenne luo ja poistakaa korkit. Etsikää putkista 1.8 ml merkkiviiva.
g. Jos otatte vettä vesijohdosta, säätäkää veden virtaus niin, että näytteenotto on helppoa.
   Muista vesilähteistä, esim. jääkaapista, voi olla tarpeen ottaa vesi ensin lasiin tai mitta-
   astiaan ja täyttää sitten putket.
h. Täyttäkää kaikki 6 putkea 1.8 ml merkkiviivaan asti.
i. Sulkekaa putket korkilla. Pankaa putket ohessa olevaan suljettavaan muovipussiin, merkit- kää päivämäärä ja veden lähde alla olevaan tilaan, ja ottakaa näytteet mukaan 9 kk käynnille. Tarkistakaa vielä, että kaikki kuusi putkea on täytetty merkkiviivaan asti ja että korkit ovat kunnolla suljetut eivätkä vuoda.

Jos Teillä on jotakin kysyttävää, soittakaa meille numeroon 02-313 1469/TEDDY-tutkimus, niin autamme mielellämme. Kiitoksia!

Keräyspäivä: _____

Merkatkaa kaikki vaihtoehdot, jotka pitävät paikkansa

_____ Kaupungin vesijohtovettä
_____ Vesijohtovettä kaivosta tai lähteestä
_____ Vesijohtovettä, lähde tuntematon
_____ Pullotettua vettä
_____ Muuta _____

_____ Suodatettua
_____ Keitettyä
_____ Tislattua

Appendix B5: TAP WATER COLLECTION INSTRUCTIONS - Spanish version

El Estudio TEDDY
Instrucciones para la Colección de Agua

Materiales

a. Seis – tubos de 2 ml para colección
b. Bolsa Ziploc para poner los tubos

Instrucciones

Nos gustaría obtener una muestra de agua de la que normalmente toma su bebé. Esta es la agua que su bebé toma en el biberón o la que mezcla con la formula infantil, cereal o jugo. Esta puede ser agua del grifo o llave, agua embotellada, agua destilada o agua de su refrigerador. Eliga el tipo de agua que su hijo/a toma mas seguido. Si usted hierve, destila o filtra el agua, sigua la misma rutina para la muestra. Por favor permita que el agua hervida se enfrie antes de llenar los tubos para la colección.

Por favor obtenga la muestra de agua en la mañana de su visita de 9 meses y traigala con usted a la clinica.

j. Lleve los seis tubos a su fuente de agua y remueva la tapa de los tubos. Localice la linea de 1.8 en los tubos.
k. Si esta tomando su muestra del grifo o llave, ajuste el flujo del agua para mayor facilidad de la colección. De otras fuentes, como del refrigerador, quizas sea necesario colocarla en un vaso primero o taza medidora luego llenar los tubos.
l. Llene cada uno de los seis tubos hasta la linea de 1.8 que esta en un lado del tubo. (Por favor asegurese de no llenar mas de la linea de 1.8; congelaremos estas muestras y si el agua sobrepasa este limite no hay suficiente espacio para expanderse)
m. Asegure las tapas en los tubos. Ponga los tubos en la bolsa Ziploc incluida, anote la fecha y la fuente del agua y traigala a su visita de 9 meses a la clinica.
n. Examine la bolsa Ziploc para asegurarse que los seis tubos estan llenos hasta la linea, y sus tapas estan bien puestas y no hay goteo.

Si tiene cualquier pregunta, por favor llame a nuestra oficina al xxxxx y estaremos felices de poderlo ayudar.
Gracias.

Fecha de colección: _____

Marque todas las que apliquen

_____Agua de grifo o llave de la ciudad
_____Agua de grifo o llave de pozo o manantial
_____Agua de grifo o llave, fuente desconocida
_____Agua embotellada
_____Otra _____

_____Filtrada
_____Hervida
_____Destilada

Appendix C1: PRE-VISIT TOENAIL SAMPLE PREPARATION INSTRUCTIONS FOR PARENTS – English version

TEDDY Study
Pre-visit Toenail Sample Preparation Instructions

We will be collecting a toenail sample from your child at the X month TEDDY visit. In order to prepare for this we would like to ask you to:

1. Please refrain from trimming your child's toenails for 3 weeks before the visit.

2. Please remove cosmetic nail polish with a commercial polish remover before the visit.

Thank you!!!!

Appendix C2: PRE-VISIT TOENAIL SAMPLE PREPARATION INSTRUCTIONS FOR PARENTS – Swedish version

Information om förberedelse för provinsamling av

tånaglar

Vid X-månadersbesöket önskar vi samla in tånaglar från ert barn. Vi vill klippa barnets alla 10 tånaglar. Som förberedelse för detta

ber vi er att:

1. Undvika att klippa barnets tånaglar minst tre veckor före besöket.

2. Ta bort eventuellt nagellack med nagellacksborttagningsmedel.

Tack!!!

Varför samlar vi in tånaglar?

I tånaglar kan man mäta selen. Selen är en s.k. antioxidant. Eventuellt kan selen och/eller andra antioxidanter ha betydelse för utveckling av antikroppar och diabetes. I TEDDY studeras även andra ämnen som räknas som antioxidanter såsom askorbinsyra, omega-3 fettsyror, mineraler och olika vitaminer.

Appendix C3: PRE-VISIT TOENAIL SAMPLE PREPARATION INSTRUCTIONS FOR PARENTS – Spanish version

Estudio TEDDY Estudio
Instrucciones para la Preparación de la Muestra de Uñas antes de la Visita

Tomaremos una muestra de uñas de los pies de su hijo en la visita TEDDY de X meses. Para que esto sea posible le pediremos que:

3. Por favor absténgase de cortar la uñas de su hijo 3 semanas antes de la visita.

4. Por favor remueva cualquier barniz cosmético con cualquier removedor de barniz comercial.

Gracias!!!!

Appendix D1: TOENAIL SAMPLE COLLECTION INSTRUCTIONS FOR PARENTS – English version

TEDDY Study
Toenail Sample Collection Instructions

Subject ID_____ Local Code _____

We would like to collect a toenail sample from your child. Please follow the instructions below for collecting the sample and sending the sample back to the TEDDY clinic.

Instructions:

1. Please only collect toenail samples, do not collect fingernail samples.
2. If necessary, remove nail polish with a commercial polish remover from your child's toenails.
3. Gently scrape debris from below the toenails with an orange stick (a stick of orangewood with tapered ends, used in manicuring) or soft tipped cuticle stick (i.e. clean under your child's toenails).
4. Cleanse the top of the toenails with rubbing alcohol.
5. Place something under your child's feet to catch the trimmings (such as a piece of paper or magazine). Trim all ten toenails to a comfortable length using either a clipper or nail scissors. Trim mostly straight across, and leave some white edge visible. Do not trim below the nail groove.
6. Place clippings in plastic container provided to you by the clinic.
7. Write the date of collection at the bottom of this sheet.
8. Place this sheet along with the plastic container inside of the envelope provided to you by the clinic and seal the envelope.
9. To send the sample back to the clinic place the envelope in your mailbox, drop-off at any US Post Office, or place in a US Post Office Express Mail drop box.

If you have any questions, please call our office at xxxxx and we will be happy to help.

Thank you!

Collection Date: _____
dd/mmm/yyyy

Appendix D2: TOENAIL SAMPLE COLLECTION INSTRUCTIONS FOR PARENTS – German version

TEDDY Study

Zehennagel-Probe

Name des Kindes_____ Geburtsdatum des Kindes_____

Gern würden wir eine Zehennagel-Probe Ihres Kindes sammeln. Bitte folgen Sie der Anleitung und senden sie die Probe an uns zurück.

Anleitung:

1. Bitte schneiden Sie die Zehennägel 3 Wochen zuvor nicht ab.
2. Wenn nötig, entfernen Sie bitte Nagellack mit normalem Nagellackentferner.
3. Entfernen Sie bitte Fremdkörper oder Schmutz unter den Nägeln.
4. Platzieren Sie ein Tuch unter den Füssen des Kindes, um die Zehennägel aufzufangen. Bitte alle 10 Zehennägel mit einem Clipper oder einer Nagelschere gerade, nicht zu tief abschneiden.
5. Die abgeschnittenen Zehennägel in den von uns bereitgestellten Plastikbehälter geben.
6. Notieren Sie bitte auf diesem Zettel (unten) das Datum.
7. Diesen Zettel und den Plastikbehälter in einen wattierten Umschlag und diesen in die TNT-Box stecken.
8. Rufen Sie den TNT-Express Service an.

Falls Sie dazu Fragen haben, können Sie uns jederzeit unter der kostenlosen TEDDY-Hotline 0800 – 33 83339 bzw. 0800 – 33 TEDDY erreichen. Wir werden Ihnen dann alle Fragen beantworten.

Vielen Dank!

Datum der Zehennagel Probe: _____

Appendix D3: TOENAIL SAMPLE COLLECTION INSTRUCTIONS FOR PARENTS – Swedish version

Instruktion för insamling av tånaglar

Subject ID_____ Local Code _____

Vi skulle vilja ha prov på ert barns tånaglar. Följ nedanstående instruktioner innan ni skickar oss provet eller lämnar provet på TEDDY-mottagningen vid ert nästa besök.

Instruktioner:

1. V g samla bara in tånaglar – inga naglar från fingrarna.
2. Om barnet har nagellack på tånaglarna, ta bort det med nagellackborttagningsmedel.
3. Tvätta barnets fötter.
4. Skrapa försiktigt bort smuts och annat från undersidan av naglarna med en ”orange pinne” eller annan mjuk pinne.
5. Rengör ovansidan av naglarna med en spritsudde.
6. Lägg något under barnets fot för att fånga upp de avklippta bitarna (t ex en bit hushållspapper eller en handduk).
7. Klipp alla tio naglarna till lagom längd med en nagelklippare eller nagelsax. Klipp rakt av och lämna en liten vit kant. Klipp inte ner till nagelfästet.
8. Lägg nagelbitarna i plasröret.
9. Skriv vilket datum ni klippte naglarna längst ned på denna blankett.
10. Lägg blanketten tillsammans med plaströret i kuverten och klistra igen.
11. Ta med kuverten till nästa TEDDY-besök eller skicka det till oss.

Datum då naglarna klipptes: _____

Om ni undrar över något så kontakta er TEDDY-sköterska!
Tack!

Appendix D4: TOENAIL SAMPLE COLLECTION INSTRUCTIONS FOR PARENTS – Finnish version

TEDDY-tutkimus
Ohjeet vanhemmille lasten varpaankynsinäytteiden keräämisestä

TEDDY-tutkimuksessa kerätään lasten varpaiden kynsistä näyte 2-vuotiskäynnin tai sitä seuraavan vastaanottokäynnin (27 kk) yhteydessä. Voitte leikata kynnet myös kotona, jos leikkaaminen on jäänyt jostain syystä tekemättä vastaanotolla. Tällöin saatte tarvittavat välineet mukaanne kotiin ja pehmustetun palautuskirjekuoren näyteputken postitusta varten.

Kynsien leikkaaminen kotona:

1. Poistakaa mahdollinen kynsilakka lapsen kaikista varpaankynsistä.

2. Puhdistakaa irtolika kynsien alta esim. puutikulla.

3. Pyyhkikää kynnet alkoholiin kastetulla vanu-, kangas- tms. tupolla.

4. Laittakaa lapsen jalkojen alle puhdas paperi, muovinpala tai muu alusta kynnenpalojen keräämistä varten. Kynnet löytyvät parhaiten tummalta alustalta.

5. Jos suinkin mahdollista, leikatkaa kaikki 10 kynttä sopivan pituisiksi TEDDY-tutkimusvastaanotolta saamillanne saksilla. Leikatkaa kynnet mahdollisimman suoraan ja jättäkää hieman valkoista reunaa jäljelle. Varokaa leikkaamasta kynsiä liian lyhyiksi. Jos ette saa leikatuksi kynsiä kaikista varpaista, muutamakin kynnenpala on arvokas tutkimuksen kannalta.

6. Kerätkää kaikki saamanne kynnenpalat ja pankaa ne valmiiksi merkittyyn kierrekorkilliseen näyteputkeen.

7. Pankaa näyteputki palautuskirjekuoreen ja postittakaa lähipäivinä.

8. Näyteputki voidaan säilyttää huoneenlämmössä tai jääkaapissa lähettämiseen asti.

E1. Salivary Cortisol Sample Collection Instructions for Parents – English version

33484

Subject ID

INSTRUCTIONS FOR COLLECTING SALIVA AT HOME

In the morning of the clinic visit we ask you to collect saliva from your child.

It is important to note that if your child has been on **oral steroids** during the last 30 days, saliva should **not** be collected. Saliva can be collected if the child has been given topical or inhaled steroids.

The saliva collection should be done:
- 30 minutes after the child wakes up,
- before the child has eaten or drunken anything **-** except water, and
- before brushing the teeth.

If your child by mistake eats or drinks anything you need to wait 30 minutes before the saliva is collected.

If your child brushed his/her teeth before collecting the saliva, the child should rinse his/her mouth with water before the saliva is collected.
Since we will be collecting saliva again at your visit, the following is important:

- Do **not** give the child anything containing **caffeine** (coke, coffee, tea, chocolate) during the day of the clinic visit.
- Do **not** give the child anything to **eat or drink** (except water) **30 minutes** before the clinic visit.

How to collect the saliva at home

Three Sorbette sticks with saliva should be collected. They are packed together in an envelope; Five Sorbette sticks are included in case you misplace a stick, but only use three sticks to collect the saliva.

1. Remove one Sorbette from the envelope. Close the envelope immediately to protect the other Sorbettes from contact with moisture.
2. Place the cap of the conical tube on a flat surface.
3. Place and hold the Sorbette under the child's tongue for at least 40 seconds. Pull out the Sorbette a bit and replace it under the tongue again until the Sorbette begins to expand (at least one minute total time). **It is very important that you hold the Sorbette firmly the whole time when you collect the saliva to avoid swallowing of the Sorbette.**
   The Sorbette can also be moved around in the mouth and lip area to collect saliva that may be drooling down the cheek or pooling in the mouth.
4. When the Sorbette is saturated, insert it tip down into the cap.
5. Place the second Sorbette under the child's tongue and repeat steps 3-4 above.
6. Place the third Sorbette under the child's tongue and repeat step 3-4 above.
7. Slide the conical storage tube over the purple Sorbette sticks and snap down securely into cap. Please be sure that the cap is screwed on to the storage tube very tightly.
8. Bring the tube to the clinic.

Please complete the Collection of Saliva Form on the next page and give it to the TEDDY staff at the visit!

E2. Salivary Cortisol Sample Collection Instructions for Parents - German version

5044

TeddyCode _____

Anleitung zur Sammlung einer SPEICHELPROBE ZUHAUSE

Wir möchten Sie bitten, am Tag der Blutentnahme, am Morgen eine Speichelprobe von ihrem Kind zu nehmen.

Bitte beachten Sie, wenn ihr Kind während der letzten 30 Tage **orale Steroide** (z.B. Prednison, Cortison, Dexamethason) bekommen hat, können Sie **keine Speichelprobe** nehmen, außer Ihr Kind bekommt topische (Salben, Cremes) oder Steroide zum Inhalieren.

Die Speichelprobe sollte genommen werden:
- **30 Minuten** nach dem Aufwachen des Kindes
- **Bevor** das Kind etwas isst oder trinkt - ausgenommen Wasser
- **Bevor** es die Zähne putzt

Wenn Ihr Kind irrtümlich etwas gegessen oder getrunken hat, warten Sie bitte 30 Minuten bis Sie die Speichelprobe nehmen.

Wenn sich Ihr Kind die Zähne geputzt hat bevor Sie die Speichelprobe nehmen, soll es sich vor der Speichelprobe den Mund mit Wasser ausspülen.

Wir werden auch Speichelproben beim TEDDY-Besuch nehmen, daher bitten wir Sie folgendes zu beachten:
- Geben Sie an dem Tag der Blutentnahme dem Kind bitte keine koffeinhaltigen Getränke (z. B. Kaffee, Cola, Tee, Schokolade)
- Geben Sie bitte dem Kind **30 Minuten** vor der Blutentnahme nur Wasser und **nichts zu essen**

Wie gewinnen Sie die Speichelprobe Zuhause?

Der Speichel soll mit Hilfe von **drei** Sorbette Stäbchen gesammelt werden. Sie befinden sich alle in einer Verpackung: Für den Fall, dass Sie ein Sorbette Stäbchen verlegen, sind 5 Sorbette Stäbchen beigefügt. Aber benutzen Sie 3 Sorbette Stäbchen, um die Speichelprobe zu gewinnen.

1. Nehmen Sie ein Sorbette Stäbchen aus der Verpackung. Schließen Sie die Verpackung bitte gleich wieder, sie schützen damit die anderen Sorbette Stäbchen vor Feuchtigkeit.
2. Stellen Sie die Verschlusskappe des Röhrchens auf eine ebene Unterlage.
3. Geben Sie den Watteteil der Sorbette für mindestens 40 Sekunden unter die Zunge des Kindes. Ziehen Sie die Sorbette ein wenig heraus und stecken sie sie wieder unter die Zunge bis der Watteteil beginnt, sich auszudehnen (mindestens eine Minute). **Bitte halten Sie den roten Stiel der Sorbette während der gesamten Speichelprobe fest.**
   Sie können mit dem Wattekopf der Sorbette auch über die Lippen streichen, um Speichel aus dem Mund zu sammeln.
4. Wenn der Wattekopf der Sorbette mit Speichel vollgezogen ist, stecken Sie die Sorbette mit der Wattespitze nach unten in die Verschlusskappe.
5. Geben Sie den Wattekopf der zweiten Sorbette unter die Zunge des Kindes und wiederholen Sie die oben beschriebenen Schritte 3-4.
6. Geben Sie den Wattekopf der dritten Sorbette unter die Zunge des Kindes und wiederholen Sie die oben beschriebenen Schritte 3-4.
7. Stülpen Sie das Röhrchen über die roten Sorbettenstiele und schließen Sie das Röhren indem es in der Verschlusskappe einrastet. Bitte stellen Sie sicher, dass die Verschlusskappe richtig fest verschlossen ist.
8. Bringen Sie das Röhrchen mit zum TEDDY-Besuch.

Füllen Sie bitte den Fragebogen zur Speichelprobe aus und geben Sie ihn bei dem TEDDY-Besuch Ihrem Betreuer, Arzt ab.

Sammlung der Speichelprobe - Elternform Page 2 of 4 Form Revision Date: 28 January 2009

E3. Salivary Cortisol Sample Collection Instructions for Parents - Swedish version

9366

Subject ID

UPPSAMLING AV SALIV I HEMMET

På morgonen samma dag som TEDDY-besöket ber vi er samla upp lite saliv från ert barn. Det är viktigt att notera att om barnet har fått **kortison** under de senaste 30 dagarna ska saliv **inte** samlas upp. Det är dock inga hinder att samla saliv om barnet har fått kortison i form av kräm eller genom inhalation.

Uppsamling av saliv ska göras:
- **30 minuter** efter att barnet har vaknat på morgonen,
- **innan** barnet har ätit eller druckit något - förutom vatten,
- **innan** barnet har borstat tänderna.

Om barnet råkar äta eller dricka något måste ni vänta 30 minuter efter detta innan ni samlar upp saliven.

Om barnet borstat tänderna innan saliven samlats upp, ska barnet skölja munnen med vatten innan saliven samlas upp.

Eftersom vi också kommer att samla upp saliv vid ert besök på TEDDY-mottagningen är följande mycket viktigt:

- Låt **inte** barnet dricka något som innehåller **koffein** (Coca Cola, kaffe, the, choklad) under dagen innan ni kommer på TEDDY-besöket.
- Ge **inte** barnet något att **äta eller dricka** (förutom vatten) 30 minuter före TEDDY-besöket.

Instruktioner för uppsamling av saliv i hemmet

Tre Sorbette-pinnar med saliv ska samlas in. De är paketerade tillsammans i ett kuvert:fem Sorbette pinnar finns i kuverten om någon skulle komma bort, men använd bara tre pinnar för att samla upp saliven.

1. Ta en Sorbette från kuvertet. Stäng kuvertet genast för att undvika att de andra Sorbette-pinnarna blir fuktiga.
2. Placera locket till det konformade röret på ett platt underlag.
3. Placera Sorbette-pinnen under barnets tunga minst 40 sekunder och håll fast den ordentligt. Dra ut Sorbette-pinnen lite och stoppa tillbaka den igen under barnets tunga till dess den börjat svälla. Det tar minst en minut innan Sorbettpinnen svällt färdigt. Det är viktigt att hela tiden hålla fast i Sorbette-pinnen för att undvika att barnet sväljer pinnen. Sorbetten kan också röras runt i munnen och kring läpparna för att fånga upp saliv som barnet dreglar eller som samlats i munnen.
4. När Sorbett-pinnen är full med saliv, placera den med toppen nedåt i locket.
5. Placera nästa Sorbette under barnets tunga och upprepa steg 3-4.
6. Placera den tredje Sorbette-pinnen under barnets tunga och upprepa steg 3-4.
7. Placera det konformade röret över Sorbette-pinnarna och tryck till så att locket sluter till om röret. Kontrollera att locket är ordentligt fastskruvat på röret.
8. Ta med röret till kliniken.

Var snäll och fyll i formuläret "Insamling av saliv - Föräldraformuläret" och ge det tillsammans med röret till TEDDY-sköterskan.

E4. Salivary Cortisol Sample Collection Instructions for Parents - Finnish version

44953

TEDDY-TUNNUS

TEDDY-tutkimus
Ohjeet vanhemmille sylkinäytteen keräämisestä kotona

TEDDY-tutkimuksessa kerätään sylkinäyte lapsilta 3,5 sekä 4,5 ja 5,5 vuoden iässä. Näyte kerätään kotona samana aamuna, jolloin lapsellanne on käynti tutkimusvastaanotolla. Jotta keräys onnistuu hyvin, seuraavat seikat on hyvä pitää mielessä:

Jos lapsellanne on ollut **steroiditablettilääkitys** (kortisoni) edeltäneen kuukauden aikana, **näytettä ei voi ottaa.** Sen sijaan sumutteena tai voiteena otettava steroidilääkitys ei ole esteenä näytteen keräämiselle.

Sylkinäyte kerätään

- 30 minuutin kuluttua lapsenne heräämisestä
- ennen kuin lapsenne on syönyt tai juonut mitään lukuun ottamatta vettä
- ennen kuin lapsenne on harjannut hampaansa.

Jos lapsenne kuitenkin syö tai juo vahingossa jotain muuta kuin vettä ennen kuin olette ehtineet kerätä näytteen, odottakaa 30 minuuttia ja ottakaa näyte vasta sen jälkeen.

Jos lapsenne ehtii harjata hampaansa ennen kuin näyte on saatu kerätyksi, huuhdelkaa huolellisesti lapsen suu ja ottakaa näyte sen jälkeen.

Myös tutkimusvastaanotolla kerätään samana päivänä kaksi sylkinäytettä, jota varten on tärkeää pitää mielessä seuraava ohjeet:

- Lapsi ei saa syödä tai juoda vastaanottopäivänä mitään kofeiinia sisältävää, ennen kuin molemmat näytteet on otettu vastaanotolla. Tällaisia "kiellettyjä" tuotteita ovat mm. kahvi, tee, suklaa, kaakao ja cola-juomat. Muita ruokia ja juomia saa nauttia vapaasti, mutta 30 minuutin ajan ennen vastaanotolle tuloa saa vain juoda vettä. Näytteiden oton jälkeen ei ole mitään rajoituksia.

Näyte kerätään seuraavasti:

Näytteen keräämiseen tarvitaan kolme Sorbette-tikkua. Teille on pakattu viisi tikkua valmiiksi kirjekuoreen, jonka saitte tutkimushoitajaltanne edellisellä tutkimuskäynnillä tai äskettäin postissa. Kaksi näistä on varatikkuja.

1. Ottakaa ensimmäinen Sorbette-tikku kirjekuoresta. Sulkekaa kirjekuori välittömästi, jotta siellä olevat neljä muuta tikkua eivät kerää kosteutta ilmasta.
2. Avatkaa kirjekuoressa mukana oleva näyteputki ja pankaa korkki ylösalaisin tasaiselle alustalle.
3. Pankaa Sorbette-tikku lapsen kielen alle vähintään 40 sekunnin ajaksi.
   Pyörittäkää tikkua myös muualla suussa, jotta siihen saadaan mahdollisimman paljon sylkeä. Ottakaa tikku sen jälkeen ulos lapsen suusta ja pankaa uudelleen lapsen kielen alle, kunnes tikun pää selvästi turpoaa. Tähän tarvitaan aikaa noin minuutin verran. **On erittäin tärkeää, että pidätte itse tikusta kiinni lujasti koko ajan, jotta lapsi ei vahingossa niele tikkua.**
4. Kun ensimmäinen Sorbette-tikku on kostunut, pankaa se putken korkkiin kostunut tikunpää alaspäin.
5. Pankaa toinen Sorbette-tikku lapsen kielen alle ja tehkää sen kanssa samoin kuin ensimmäisen tikun kanssa.
6. Pankaa kolmas Sorbette-tikku lapsen kielen alle ja tehkää sen kanssa samoin kuin ensimmäisen tikun kanssa.
7. Liu'uttakaa näyteputki korkissa olevien tikkujen päälle ja painakaa se tiukasti kiinni korkkiin. Varmistakaa myös, etta kierrätte korkin tiukasti kiinni säilytysputkeen.
8. Tuokaa putki mukananne vastaanotolle.

Lopuksi, täyttäkää ystävällisesti oheinen näytteen keräämiseen liittyvä lomake ja tuokaa sekin mukananne vastaanotolle.

F1. Information for Parents on Caffeine Content of Beverages, Foods and Drugs to Avoid Giving to Child Before Salivary Cortisol Sample Collection – US products

References:
1 Beverage Partners Worldwide, 2007; The Coca-Cola Co., 2007; Monster Beverage Co., 2007; PepsiCo Inc., 2007; Redux Beverages, 2007; Rockstar, 2007; USDA National Nutrient Database for Standard Reference, 2007

2. http://www.ific.org/publications/brochures/pregnancybroch.cfm

3. Center for Science in the Public Interest, 2007; Haagen-Dazs, 2007; The Hershey Co., 2007; Vroom Foods Inc., 2007

Coffee
Drip, regular 106-164 mg./ 150 ml
Percolated, regular 93-134 mg./ 150 ml
Instant, regular 47-68 mg./ 150 ml
Decaffeinated 2-5 mg./ 150 ml

Loose-leaf Tea (imported tea)
Black 25-110 mg.
Oolong 12-55 mg.
Green 8-36 mg.

Tea (black tea assumed)
Brewed, major U.S. brands 20-80 mg.
1 minute brew 21-33/mg./ 150 ml
3 minute brew 35-46 mg./ 150 ml
5 minute brew 39-50 mg./ 150 ml
Canned iced tea 22-36 mg./ 150 ml
Iced tea 67-76 mg./ 360 ml
Instant tea 22-36 mg./ 150 ml

Cocoa and Chocolate
Cocoa Beverage (mix) 2-8 mg./ 180 ml
Milk Chocolate 6 mg./ 30 ml
Baking Chocolate 35 mg./ 30 ml
Sweet Chocolate 20 mg./ 30 ml
Ovaltine 0 mg.
Postum 0 mg.
Hershey's Chocolate Bar, 9mg/ 43.4 g
Hershey's Special Dark Chocolate Bar, 18 mg/ 40.6 g
Chocolate-flavored syrup 4 mg /30 ml

Sodas
A&W Cream Soda 29 mg/360 ml

Mountain Dew 54 mg./ 360 ml
Code Red Mountain Dew 54 mg./ 360 ml
Diet Mountain Dew 54 mg/360 ml
Coca Cola, Diet Coke 46 mg./ 360 ml
Dr Pepper, Diet Dr. Pepper 41 mg./ 360 ml
Cherry Coca-Cola, Diet Cherry Coca-Cola 35 mg/360 ml
Tab 45 mg./ 360 ml
Shasta Cola 44 mg./ 360 ml
Mr. Pibb 41 mg./ 360 ml
Mr. Pibb, Diet 57 mg./ 360 ml
Dr. Pepper 40 mg./ 360 ml
Pepsi Cola 38 mg./ 360 ml
Wild Cherry Pepsi 38 mg/360 ml
Diet Wild Cherry Pepsi 38 mg./ 360 ml
Pepsi Light, Diet 36 mg./ 360 ml
Diet Right Cola 36 mg./ 360 ml
Mello Yello 53 mg./ 360 ml
Royal Crown Cola 36 mg./ 360 ml
Craigmont Cola 0 mg.
7-Up 0 mg.
Sprite, Sprite Zero 0 mg.
Fanta 0 mg.
Fresca 0 mg.
Root Beer 0-23 mg / 360 ml
Club Soda 0 mg.
Ginger Ale 0 mg.
Tonic Water 0 mg.
Orange Soda 0 mg.
Grape Soda 0 mg.
Sunkist Orange Soda 41 mg/360 ml

Other foods
Foosh Energy Mints, 1 mint, 100
Haagen-Dazs Coffee Ice Cream, 20 mg per 106 g
Jolt Caffeinated Gum, 33mg per stick
NoDoz Maximum Strength, 200 mg per tablet
Starbucks Coffee Ice Cream, 50-60 mg per 106 g
AMP Tall Boy Energy Drink, 143 mg per 480 ml
Enviga, 100 mg per 360 ml
Full Throttle, 144 mg per 480 ml.
Full Throttle Fury, 144 mg per 480 ml.
Monster Energy, 160 mg per 480 ml.
No Name (formerly known as Cocaine), 280 mg per 252 ml
Red Bull, 76 mg per 252 ml
Rockstar, 160 mg per 480 ml
SoBe Adrenaline Rush, 152 mg per 480 ml

SoBe No Fear, 174 mg per 480 ml
Vault, 47 mg per 240 ml

Non-prescription Drugs
Caffedrine Capsules 200 mg.
NoDoz Tablets 200 mg.
Vivarin Tablets 200 mg.

Pain Relievers
Anacin Analgesic 64 mg.
Cope 32 mg./ tablet
Bufferin 0 mg.
Excedrin 130 mg.
Midol 64 mg.
Plain Aspirin 0 mg.
Tylenol 0 mg.
Vanquish 66 mg.

Diuretics (standard dose)
Aqua Ban 200 mg.
Fluidex 0 mg.
Permathene Water Off 200 mg.
Pre-Mens Forte 100 mg.

Cold Remedies
Actifed 0 mg.
Contac 0 mg./ tablet
Comtrex 0 mg.
Coryban-D 30 mg.
Dristan 30 mg.
Neo-Synephrine 15 mg.
Sudafed 0 mg.
Triaminicin 30 mg.
Excedrin, Extra Strength, 2 130 mg per 2 tablets

Prescription Drugs
Dristan 30 mg.
Neo-Synephrine 15 mg.
Sudafed 0 mg.
Triaminicin 30 mg.

F2. Information for Parents on Caffeine Content of Beverages, Foods and Drugs to Avoid Giving to Child Before Salivary Cortisol Sample Collection – German products

FOODS, BEVERAGES

Milk/Cheese products

Eiskaffee 1,5%F,Milchunion Hocheifel,MUH	Coffee
Joghurt m.Kaffeezubereitung,Kaefer	Coffee
Espresso Joghurtdessert,Milchw.Mainfrank	Coffee
Exquisa Latte Macchiato,0,1%F,Karwendel	Coffee

Dessert mixture

Tiramisupulver,Dr.Oetker	Coffee
Creme Tiramisu,P,Dr.Oetker	Coffee

Beverages

Apfel-Eistee,Glockengold	Tea (black)
Apfelessig-Holunder,Active Drink,Jacobi	Tea (black)
Cappuccino Caramel-Krokant,Krueger	Coffee
Cappuccino Specials Daim,Jacobs/Kraft	Coffee
Cappuccino Specials Toblerone,KraftFoods	Coffee
Cappuccino-Pulver,Deutsch Extrakt-Kaffee	Coffee
Cappuccino-Pulver,o.Zucker,Nestle	Coffee
Coca Cola	Caffeine
Cola Mix,Euroshopper,Heemann	Caffeine
Cola,Pepsi light	Caffeine
Cola-Getraenke	Caffeine
Diaetlimonade Schwipp Schwapp,PepsiCo	Caffeine
Eiskaffee,Pulver,Krueger	Coffee
Eistee m.Suessstoff,Trendy Plus	Tea (black)
Eistee,Pfirsich,Zitrone	Tea (black)
Eistee,Waldfrucht,Nestea,Nestle	Tea (black)
Family White Cappuccino,Krueger	Coffee
Gruentee-Getraenk,Zitrone,Fruity	Tea (black)
Ice Tea Lipton,Pfirsich,Unilever	Tea (black)
Mezzo Mix Zero,Coca Cola Company	Caffeine
Mezzo Mix,Fanta m.Cola 1:1	Caffeine
MV-Getraenk,Raktiv	Caffeine
Nescafe Latte Macchiato,Nestle	Coffee
Pfirsich-Getr.pulver,Krueger	Tea (black)
Red Bull,zuckerfrei,Red Bull GmbH	Caffeine
Schoko&Cappuccino,Pulver,Krueger	Coffee
Veltins V+Cola,Veltins	Caffeine
Zitronenteegetraenk,Nestea	Tea (black)
Zitronenteepulver,Pfirsichteegetr.,o.Vit	Tea (black)
Zitronenteepulver,Teka Quick	Tea (black)

Chocolate, candies, ice

Sahne-Mocca-Schokolade,Feodora	Coffee
Gefuellte Schoko.,Latte Macchiato,Sarott	Coffee
Belminis Cafe Macchiato,Zentis	Coffee
Eiskrem Cappuccino m.Schoko-Nougatsplit	Coffee
Tiramisu Eis,Cremissimo,Langnese	Coffee

DRUGS

analeptics

Halloo-Wach® N, Nycomed Deutschland

analgesics /Antirheumatika, Pain Relievers

Aspirin® forte; Bayer Vital
Azur® compositum, Steiner
Azur®; Steiner
Chephapyrin® N, MIP Pharma
COPYRKAL®; Berlin-Chemie
dolomo® TN, Astellas Pharma
EUDORLIN® Schmerztabletten; Berlin-Chemie
HA-Tabletten N® gegen Schmerzen, Boehringer Ingelheim
Melabon® K, Medice
Neopyrin® forte; RIEMSER
Neuralgin® Schmerztabletten, Pfleger
Novo Petrin® Novum Schmerztabletten, OTW-Naturarzneimittel
Octadon® P; UCB
Optalidon® N, Novartis Consumer Health
Prontopyrin® plus; McNeil CH
ratiopyrin® Schmerztabletten ratiopharm
Saridon®, Bayer Vital
Thomapyrin® INTENSIV; Boehringer Ingelheim
Thomapyrin® Schmerztabletten; Boehringer Ingelheim
TITRALGAN® gegen Schmerzen; Berlin-Chemie
Togal® Kopfschmerz-Brause + Vitamin C; Togal
Vivimed® mit Coffein gegen Kopfschmerzen; Mann

Influenza medicament

Grippostad® C Hartkpaseln; STADA

Neural therapeutic

Hewedolor plus Coffein; Hevert

Migraine medicament

Cafergot® N Zäpfchen; Novartis Pharma

Roborantia/Tonika

Dia-Aktivanad®-N Saft; Medice
Aktivanad®-N Saft; Medice

G. Model letter to parent for home finger stick sample

(date)
(parent address)
RE: (child's name)

Dear (parent contact name):

Thank you for collecting a home finger stick sample for the TEDDY Study. This allows us to continue to test your child for autoantibodies.

As you may recall, all the children in TEDDY are at increased risk for getting type 1 diabetes. This testing will give you important information about your child's current risk. It also helps us better understand this disease. Every child who joined the TEDDY study is an important piece of the puzzle - TEDDY's goal to find out why some children get type 1 diabetes and others do not.

Thank you for your contributions to the TEDDY Study. Support from people like you is what makes TEDDY possible and moves us towards preventing type 1 diabetes.

If you have any questions, please call us at (XXX.XXX.XXXX) or for toll-free 1-###-###-####.

Regards,

(Staff Name)
(Staff Title)

H. Model instructions to parent for home finger stick sample

TEDDY Study

Parent Instructions for Home Finger Stick Sample

CONTENTS INCLUDE:

- Return envelope with prepaid postage
- Blood Sampling Kit
  - Gloves
  - Two lancets
  - Gauze, alcohol pads, and 2 band aids
  - Blood collection tube
  - Padded 2x3 inch plastic bag

If you prefer, we can walk you through a finger stick over the phone or perform it in our clinic for you.

If you have any questions, please call us toll free at ##.

GETTING THE SAMPLE

1. Warm your child's finger with a wet washcloth for several minutes. This should leave the area warm and pink. The area used should not be swollen or previously punctured.
2. With the alcohol pad, clean the finger where the lancet will be used. Let it dry fully.
3. Pull off and discard the protective cap of the lancet. Caution: once the cap is off, the needle can be set off easily.
4. Position the child's hand downward below the child's heart to increase blood circulation.
5. Place the lancet **firmly** and squarely on the finger in the area you have prepared and release the needle. We ask that only adults handle the lancets to avoid injury.

Arrows indicate best places to poke, just to the side of the fingers.

6. After poking, gently pinch and squeeze the skin surrounding the puncture site to increase blood flow. It may be necessary to gently "milk" the finger starting at the palm of the hand to move the blood toward the end of the finger. **Let a drop form on the finger before trying to add it to the tube.** Fill the tube to the marked line approx. 5-10 drops of blood. If the blood stops flowing, use the provided gauze pad to "pull" downward on the finger toward the puncture site to get the blood flowing again.

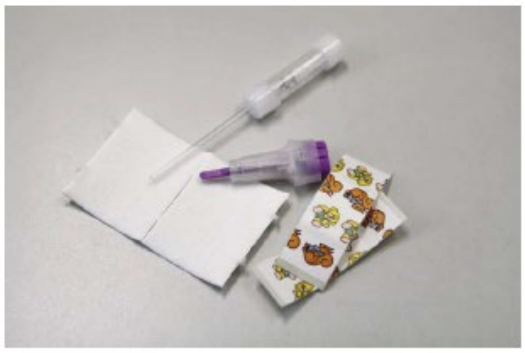
7. When the tube is filled, tightly put the cap on the tube. Place the gauze pad on your child's finger. Hold solid pressure for one minute to stop bleeding. Lifting the child's hand in the air above the heart can assist in this process. A bandage is included if necessary. All materials can be thrown away in your regular trash.
8. Place the filled collection tube in the padded 2x3 inch plastic bag. Be sure the tube is completely surrounded by the padding.
9. Seal the 2x3 inch plastic bag and write the draw date on the label. Put the bag containing the blood sample in the prepaid return envelope. Seal and put in regular mail. Please mail the same day you do the sample. No additional postage is necessary.

I. Site Specific Instructions to Parent for Home Finger Stick Sample: Germany

Tipps für die kapillare Blutentnahme

Material

Handschuhe
Tupfer
Pflaster
Hautesinfektionsmittel
Safety Lanzette Super
Microvette® 200µl
Abwurfbehälter
Patientenfragebogen mit Barcode



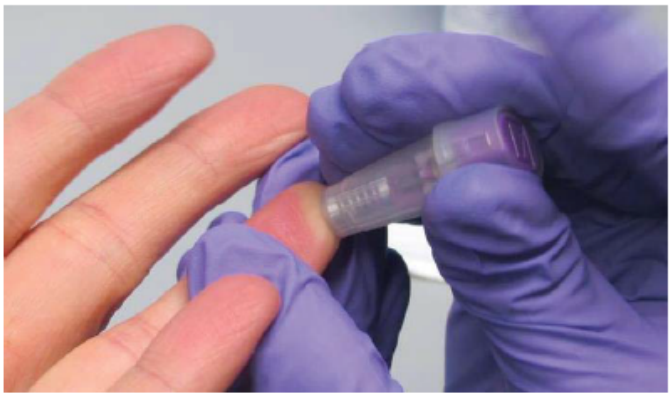
Vorbereitung des Kindes

Achten sie darauf, dass das Kind warme Hände hat und bequem sitzt.. Eventuell ist es nötig, die Hände vor der Punktion zu erwärmen. Bewährt haben sich hier folgende Methoden:

- Mit warmem Wasser planschen lassen.
- Die Hände für etwa 5 Minuten in ein feucht-warmes Tuch einschlagen.
- Fingerspiele, Knete, etc.

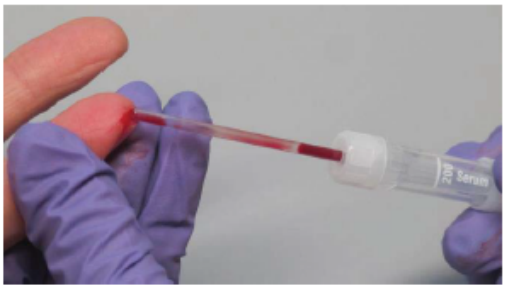
Punktion

- Entfernen Sie die Schutzkappe durch Abdrehen von der Safety-Lanzette.
- Punktieren sie an der seitlichen Fingerbeere
- Setzen Sie die Lanzette fest auf die zu punktierende, desinfizierte Stelle auf und drücken sie kräftig auf den Auslöser
- Verwerfen Sie die gebrauchte Safety-Lanzette.
- Bitte wischen Sie den ersten Blutstropfen mit einem trockenen Tupfer ab, danach kann mit der Blutentnahme begonnen werden.



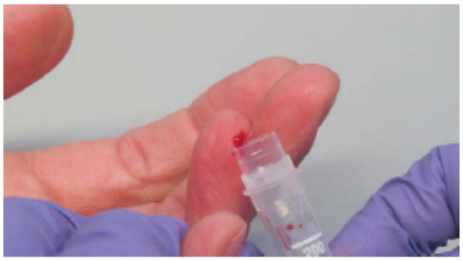
Blutentnahme mit der End-to-End Kapillare

- Halten Sie die Microvette® leicht geneigt oder horizontal und nehmen Sie das Blut mit der Kapillare auf
- Ist die Kapillare gefüllt oder nimmt wegen Luftblasen kein Blut mehr auf halten Sie die Microvette® senkrecht damit das Blut abfließen kann. Anschließend kann die Kapillare bei Bedarf wieder Blut ansaugen.



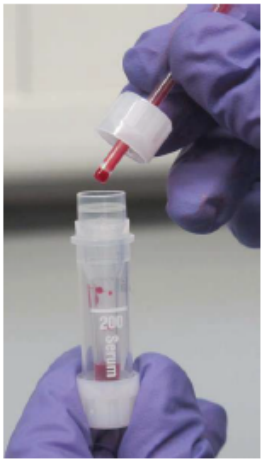
Alternativ: Blutentnahmemit dem Abtropfrand

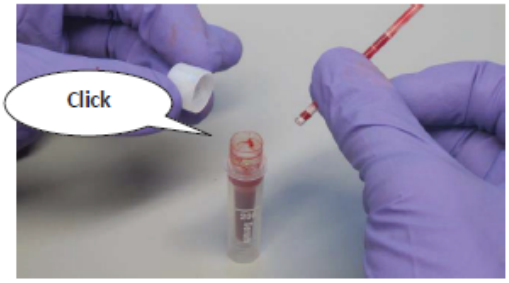
Alternativ können Sie die Verschlusskappe mit der Kapillare auch entfernen und das Blut über den Abnahmerand in das Gefäß tropfen lassen.



Ende der Blutentnahme

- Die Blutentnahme ist beendet, wenn das Röhrchen mindestens bis zur 200µl Markierung gefüllt ist.
- Zum Schluss wird der Deckel mit der Kapillare durch drehen entfernt und verworfen
- Die Microvette® wird mit dem Deckel vom Gefäßboden verschlossen. Der Deckel muss hörbar einrasten.

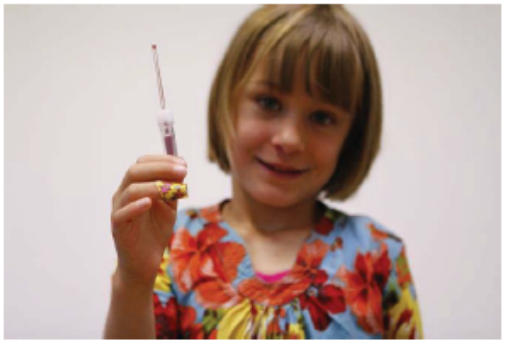




Tipps für ein gutes Gelingen

- Achten Sie darauf, dass die Hände des Kindes warm sind – der Blutfluss wird dadurch deutlich erhöht. erhöht.
- Das Blut verläuft weniger und lässt sich besser aufnehmen, wenn Sie die Punktionsstelle vorher sehr dünn mit Vaseline eincremen.
- Halten Sie die Punktionsstelle nach unten – die Schwerkraft hilft mit
- Vermeiden Sie einen zu starken Druck auf die Finger – streichen Sie die Hand immer wieder zur den Fingerspitzen hin vorsichtig aus, damit wieder Blut nachlaufen kann.
- Für eine sichere Auswertung der Probe ist es nötig, dass mindestens 200µl Kapillarblut im Röhrchen sind!

Vielen Dank für ihre Unterstützung!



J. Draft of Talking Points on Increased Blood Volume IRB, Staff, and Families (from Georgia Site)

IRB Response:

Type 1 diabetes (T1D) is a debilitating chronic autoimmune disease that is characterized by destruction of the pancreatic islet beta cells. The etiology and pathogenesis of the disease process remains elusive. The TEDDY study, our long-term prospective NIH-funded T1D consortium study, was designed and the protocol written and approved in 2004. Since then, science and technologies have evolved which have enabled the application of new applications to investigate possible mechanisms in the blood (proteomics, genomics, metabolomics, transcriptomics etc) which may give us greater insight into the etiology of the disease.

Some examples of the new technologies that TEDDY is exploring for analysis are:
. The 2 million peptide chip
. Luminex-based multiplex serodiagnostics
. Immune repertoire sequencing
. Oligonucleotide ligation assays, padlock, proximity probes and super rolling circle amplification
. Nucleic Acid Programmable Protein Arrays for Tracking Global Immune Responses

The study is closed to newborn recruitment and the cohort is being prospectively followed. Most children are now between 5 and 10 years. With the older children, more blood can safely be obtained (well within allowed limits) to enable such studies to be completed.

Talking Points for Staff and Families:

- The blood volume we collect as part of the study will be increasing later this year

More info: when time, comfort and size allows, we will collect up to 50 ml of blood, which is just under 3.5 tablespoons

- The amount of blood we draw will always be safe for the TEDDY kids.

More info: minimal risk guidelines define safe blood draws for children in research as anything under 3 mL per kg of body weight. Any child weighing over 36.8 lbs can have that amount of blood drawn safely, and we weigh each child at every visit.

- Our TEDDY children are big now. The concerns we had with the blood volume in the past was because they were little.

- As a 15 year study, we have found the science and technology change often. The advances in science that are coming up now are not ones that were available 10 years ago when TEDDY started. The TEDDY investigators are finding there are new and innovative methods that will help us to answer our study questions.

(for more, see IRB memo above)

Volume Visual #1:

Volume Visual #2:

K1. Tooth Collection Instructions - Washington

TEDDY Study
Tooth Collection Instructions

Subject ID_____ Local Code_____

We would like to collect a tooth from your child to analyze for possible environmental exposures. When your child loses one of their primary teeth, please put it in the attached "tooth box" and baggie and bring to your next TEDDY visit.

- Please do not clean the tooth
- Write down the date the tooth fell out
- Please store the tooth at room temperature

If you have any questions, please call our office at 888-324-2140 and we will be happy to help.

We have also included an optional letter your child can leave for the Tooth Fairy explaining how much this tooth can help the TEDDY scientists.

Thank you!

Date tooth came out/was removed: _____
dd/mm/yyyy

K2. Tooth Collection Instructions – Germany

Milchzähne

Liebe TEDDY Familien,

Um die Knochenzusammensetzung der TEDDY Kinder untersuchen zu können, würden wir gerne einen oder mehrere Milchzähne der TEDDY Kinder sammeln.

Milchzähne bilden, ähnlich wie Bäume, Wachstumsringe. Mit neuen Technologien wird es so möglich sein, Belastungen durch Metall und weitere Umwelteinflüsse, durch die gesamte Kindheit hindurch und auch schon vor der Geburt, anhand der Zähne zu analysieren.

Vielen Dank für Ihre Mithilfe!

Mit freundlichen Grüßen

Ihr TEDDY Team

Subject ID:_____ Local ID:_____

Anleitung zum Sammeln von Milchzähnen

Um Umwelteinflüsse und die Knochenzusammensetzung im Laufe der Kindheit untersuchen zu können, würden wir auch gerne die Milchzähne Ihres Kindes untersuchen. Daher bitten wir Sie, zusätzlich einen ausgefallenen Milchzahn Ihres Kindes für uns zu sammeln.

Gehen Sie bitte folgendermaßen vor:

1. Der Zahn darf gesäubert werden, sollte aber nicht gründlich gewaschen oder in Flüssigkeit gelagert werden.

2. Den ausgefallenen Zahn lagern Sie bitte bei Raumtemperatur in dem von uns bereitgestellten Plastikröhrchen und notieren das Datum, an dem der Zahn ausgefallen ist.

3. Den Zahn, sowie das ausgefüllte Formblatt können Sie mit der Post oder einer der nächsten Proben wieder an uns zurückschicken.

4. Bitte schicken Sie uns den Zahn nur zu, wenn Sie das Ausfalldatum kennen. Ohne ein ungefähres Datum können wir den Zahn leider nicht verwerten.

Datum, an dem der Zahn ausgefallen ist/ gezogen wurde: __ __ / __ __ __ / __ __ __ __
T T / M M M / J J J J

Falls Sie dazu Fragen haben, können Sie uns jederzeit unter der kostenlosen TEDDY-Hotline 0800 – 33 83339 erreichen. Wir werden Ihnen dann gerne alle Fragen beantworten.

Vielen Dank für Ihre Mithilfe!

K3a. Tooth Collection Instructions – Colorado

TEDDY Study
Tooth Collection Instructions

Subject ID_____ Local Code_____

We would like to collect a tooth from your child to measure an exposure to metal. Please follow the instructions below for collecting the tooth sample.

Instructions:

1. Please collect the tooth when it naturally falls out.
2. You do not need to wash the tooth.
3. Write down the date the tooth falls out.
4. Please store the tooth in a dry container and bring it to your next TEDDY visit

If you have any questions, please call our office at 303.724.7577 and we will be happy to help.

Thank you!

Collection Date: _____
dd/mm/yyyy

K3b. Tooth Collection Instructions – Colorado (Spanish)

Estudio TEDDY
Instrucciones de recolección de dientes

ID del Sujeto_____ Código Local_____

Nos gustaría colectar un diente de su hijo para medir la exposición al metal. Por favor, siga las instrucciones a continuación para recolectar la muestra de diente.

Instrucciones:

1. Por favor recoja el diente cuando se caiga naturalmente.
2. No es necesario lavar el diente.
3. Escriba la fecha en que se cayó el diente.
4. Guarde el diente en un envase seco y llévelo a su próxima visita de TEDDY.

Si tiene alguna pregunta, llame a nuestra oficina al 303.724.7577 y estaremos encantados de ayudarle.

¡Gracias!

Fecha de recolección: _____
día/mes/año

K4. Tooth Collection Instructions – Florida

Initials: _____ Vial Barcode: _____

Subject ID: _____ Local Code: _____

Primary Tooth Collection

The TEDDY Study is asking each TEDDY subject to save at least one primary tooth when it naturally falls out. Analysis of the teeth will provide a record of environmental exposures throughout the child's life thus far since the teeth form daily growth rings.

You can place it in the vial provided – please do not wash or do anything else to the tooth. Please keep the tooth at room temperature until you return it to our office.

Date of Collection: _____

K5. Tooth Collection Instructions – Sweden

170901

TEDDY

Instruktioner för insamling av mjölktänder

Ny teknologi har gjort det möjligt att bestämma inlagringar av metall i mjölktänder. Analyser kan visa på vilka metaller som barnet varit exponerat för både under tiden som foster och under sin uppväxt.

TEDDY skulle därför vilja samla in en mjölktand vid ett för barnet lämpligt tillfälle. Tanden läggs i medföljande rör och datum när den föll ut skrives på lappen. Tanden tas med vid nästa TEDDY besök.

Om ni undrar över något så kontakta er TEDDY sjuksköterska.

Tack!

K6. Tooth Collection Instructions – Georgia

Initials: _____ Vial Barcode: _____

Subject ID: _____ Local Code: _____

Primary Tooth Collection

The TEDDY Study is asking each TEDDY subject to save at least one primary tooth when it naturally falls out. Analysis of the teeth will provide a record of environmental exposures throughout the child's life thus far since the teeth form daily growth rings.

You can place it in the vial provided – please do not wash or do anything else to the tooth. Please keep the tooth at room temperature until you return it to our office.

Date of Collection: _____

K7. Tooth Collection Instructions – Finland

4.6.2018

Hyvä TEDDY-tutkimukseen osallistuva perhe!

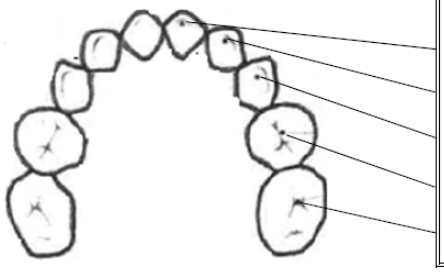
TEDDY-tutkimuksessa tutkimme erilaisten ympäristötekijöiden osuutta tyypin 1 diabeteksen kehittymiseen. TEDDY-tutkimuksessa olemme nyt aloittamassa maitohampaan keräystä tutkimuslapsilta. Tavoitteenamme on kerätä ainakin yksi maitohammas jokaiselta TEDDY-tutkimuksessa mukanaolevalta lapselta.

Maitohampaista voidaan määrittää nykytekniikalla erilaisia ympäristöaltisteita. Maitohampaasta saadaan altistetietoa jopa syntymää edeltävältä ajalta - hampaiden muodostuminen alkaa sikiöllä jo neljännellä raskausviikolla ja lapsen syntyessä maitoetuhampaiden kruunut ovat lähes kokonaan mineralisoituneet, eli ne ovat ikenen sisällä lähes valmiiksi kehittyneet.

Maitohampaista on tarkoitus tutkia mm. altistumista eri metalleille sekä analysoida luun eri ainesosia.

Toivomme, että seuraavan kerran, kun lapseltanne irtoaa mikä tahansa maitohammas, ottaisitte sen talteen sellaisenaan – hammasta ei tarvitse pestä. Hammas tulee säilyttää huoneenlämmössä, valolta suojattuna. **On tärkeää, että kirjaatte ylös hampaan irtoamispäivämäärän**. Tämä on tutkimukselle oleellinen tieto. Ottakaa ystävällisesti maitohammas mukaanne tullessanne seuraavan kerran vastaanotolle.

Kiitos vaivannäöstänne!



HAMMASTYYPPI	*MAITOHAMPAIDEN IRTOAMISIKÄ (VUOSINA)*	
	ALALEUKA	*YLÄLEUKA*
ensimmäiset etuhampaat	*5–7*	*6–8*
toiset etuhampaat	*6–8*	*7–9*
kulmahampaat	*9–11*	*10–12*
ensimmäiset poskihampaat	*9–12*	*10–12*
toiset poskihampaat	*10–13*	*11–13*

Maitohampaiden irtoamisikä

versio 2 (19.1.2018)

L1. Tooth Fairy Letter - Washington

Dear Tooth Fairy,

I know you really like to collect my teeth and I DO like the money you leave! I have a question: This time can I keep my tooth and you still leave me money? You see, I am part of a very important research study called TEDDY and the scientists want my tooth to help figure out what might cause some kids to get diabetes. I would really like to help them, so can we make a deal, and I'll give my tooth to the TEDDY scientists?

Thank You

L2. Tooth Fairy Letter – Colorado

Dear Tooth Fairy,
I am writing you a letter because I know that you are here to collect my tooth. I know that these teeth mean a lot to you, but I was wondering if I could keep it? I am part of a research study called TEDDY to find out more about childhood diabetes. They would like my tooth to help them further their research. If you can live without it, I would love to be able to give it to them to help more.
Thank You,

_____

M1. Home Glucose Testing Instructions – Colorado

Blood Glucose Testing- Frequently Asked Questions

Why are we checking blood sugar?
You have been given a glucometer and urine test strips because your child is positive for diabetes auto-antibodies. Auto-antibodies develop in the blood before a person gets type I diabetes. They indicate the immune system may be damaging the insulin-making cells in the pancreas. Having these auto-antibodies does not mean that your child will definitely get diabetes but we do think their risk of developing diabetes in the future is significantly increased. Testing your child's blood sugar will help you monitor them at home. Unfortunately we cannot stop a child from developing diabetes if they are going to get it, but the earlier we catch it the easier it is to treat and control.

When should you test blood sugars?
We recommend checking your child's blood sugar at least 2-4 times a month and daily if they are ill. It is most informative if you **check the blood sugar I the evening, 2 hours after eating**, but you can check the blood sugar any time it's convenient for you and your child. Remember to always have your child wash their hands with soap and water before testing to prevent any false readings.

What should my child's blood sugar be?

HOME GLUCOSE TESTING			
Time blood glucose (BG) was tested	**Normal BG**	**Elevated BG**	**HIGH BG** **Call TEDDY or health care provider**
Fasting No food or drinks with any sugar for at least 8 hours	**Below 100**	**100-125**	**126 or higher**
2 hours after meals	**Below 140**	**140-199**	**200 or higher**

What if my child's blood sugar is high?
If your child's blood sugar is over 200 or the glucometer says HI, wash your child's hands with soap and water and test again. If it is still >200, please call the TEDDY clinic at 303.724.7577 and your pediatrician. On the weekends or evenings, please page the on-call Barbara Davis Center doctor at 303-388-2626. **If the meter continues to say HI, call your pediatrician and go to an emergency room.**

When should I check my child's urine?

If your child gets sick and is throwing up, we recommend checking their urine for glucose and ketones with the Ketodiastix. Vomiting can be a sign of ketoacidosis, a serious complication of diabetes. Have your child urinate into a cup or container (it doesn't need to be sterile). Dip the end of the strip with the 2 squares into the urine completely. Compare the color of the squares to the corresponding color chart on the side of the container. If the strip indicates that your child has any glucose or ketones in their urine, please call us as soon as possible.

What else should I look for?

Symptoms of diabetes can appear gradually or suddenly depending on the child. Please watch for the following symptoms:

Excessive thirst
Excessive urination
Bed wetting
Not wanting to eat much but wanting to drink
Loss of energy
Behavior changes
Vomiting without diarrhea or fever
Heavy breathing

If you notice any of these symptoms, check a blood sugar and call the TEDDY clinic 303-724-7577 and your pediatrician right away.

On nights and/or weekends, please contact the on-call Barbara Davis Center doctor at 303-388-2626. PLEASE IDENTIFY YOUR CHILD AS A BDC PATIENT IN THE TEDDY STUDY.

What will happen if my child is diagnosed with diabetes? Are we out of the study?

Your child's participation in the TEDDY Study ends when diagnosed with diabetes. There may be other new onset studies available, you will be given information about any other studies.

M2. Home Glucose Testing Instructions – Swedish

Högt blodsocker – vad händer nu?

Följande blodsocker är normalt:
Fastande under 6.0
2 timmar efter måltid under 8.2

Följande blodsocker tyder på diabetes:
Fastande över 7.0
2 timmar efter måltid över 12.2

Ditt barn har haft ett blodsocker över gränsvärdena utan symtom:

Testa blodsocker:
1. när barnet är fastande på morgonen och
2. två timmar efter måltid, helst efter middagen på kvällen.

Fortsätt som ovan:

☐ 3-7 dagar

☐ en dag varannan vecka

Vid sjukdom tag något blodsockervärde slumpmässigt under dagen så länge barnet är sjukt.

Tänk på att tvätta händerna innan provtagning. Det är viktigt att stickfingret är rent!

Kontakta er sjuksköterska om:
1) två blodsocker över 12.2 registrerats
2) ett blodsocker över 16 registrerats

Vardagar, dagtid: Ring i första hand din sjuksköterska telefonnummer..... i andra hand doktor Helena på 040-337676. Övrig tid sök barnakuten.

Kontakta barnakuten på ert sjukhus om:

Barnet börjat kissa eller dricka mycket eller uppvisar onormal trötthet

Telefonkontakt med din sjuksköterska datum: .....
Local ID.....

20140924

Datum	Fastande	2 timmar efter måltid	Ev.kommentar

20140924

M3. Home Glucose Testing Instructions – Finnish

HOME GLUCOSE MONITORING

FIN all clinical centers:

If child is having T1D autoantibodies and the family is very anxious, we will ask if they would like to have the glucometer. We always offer the meter if child is having impaired glucose tolerance. It is quite typical that families take the meter home when child is already having some symptoms.

In Oulu and Tampere Clinical Centers, study nurses teach the family to use the meter. In Turku Clinical Center, laboratory staff is responsible for teaching. In Finland, we practice injecting together with the family, study the reference values and BG results and how to dispose the waste correctly. They advise families about high values/what to do and when the family should contact the child outpatient clinic. If some more special instructions are needed, study doctor is contacted. Often this teaching process is done when child is coming for OGTT visit. We always tell them to contact us, if they have any questions related to home glucose monitoring. Glucometer contains the instruction sheet how to use it correctly and three FIN Centers have own instructions for families.

If blood glucose is temporarily elevated - instruction for the family (Turku, Finland version)

Symptoms of type 1 diabetes appear gradually when autoimmune destruction of insulin producing pancreatic beta cells proceeds and insulin production begins to drop off gradually. In both DIPP and TEDDY study, BG levels of study subjects are followed regularly. Sometimes developing type 1 diabetes is revealed by chance when urine sample is analyzed or blood glucose is measured.

Insulin is essential hormone for life and therefore it is important to start insulin treatment immediately if the body does not produce enough insulin. Glucose metabolism of the child is always actively studied and followed if there is even the slightest doubt about developing diabetes.

Infection may increase the blood glucose level, but most often it is just a sign of overstimulated stress-hormone response of the body. However, it may be the first sign of decreasing insulin production. Therefore,

1. in the beginning we will follow blood glucose levels at clinic to make sure that blood glucose will be within the normal range again
2. we can give glucometer to follow blood glucose levels at home
1. when child is health again, we will perform OGTT. We will also analyze autoantibodies related to type 1 diabetes.

Home Glucose measurement – instructions:

MEASUREMENT	HOW OFTEN		PLEASE, CONTACTCHILD OUTPATIENT CLINIC
FASTING BG	_____ times per week	**IF >7 mmol/l,** BG needs to be measured during one day prior all meals and next morning	**If fasting BG 2 times >7 mmol/l or whatever BG value >11 mmol/l** Child outpatient clinic: tel. 02-313 1420 Department UB5: tel. 02-313 1418
POST-MEAL BG 1.5-2 h after meal	_____ times per week		
IF EXCESSIVE THIRST/ FREQUENT URINATION	Always		

Jos verensokeri on tilapäisesti ollut koholla - ohje perheelle (Turku, Finland version)
luonnos KNS 29.8.2011

Tyypin 1 diabeteksen oireet ilmaantuvat vähitellen, kun insuliinia tuottavien haiman beetasolujen autoimmuunituho etenee ja oma insuliinituotanto asteittain vähenee. DIPP- ja TEDDY-tutkimuksissa seurataan säännöllisesti verensokeritasoja lapsilta, joilla on perintötekijöidensä puolesta tavallista suurempi riski sairastua diabetekseen. Joskus kehittymässä oleva diabetes paljastuu sattumalta virtsatutkimuksen tai verensokerimittauksen yhteydessä.

Insuliini on elämälle välttämätön hormoni, ja insuliinihoito on tärkeätä päästä aloittamaan heti, kun oma insuliinituotanto ei enää riitä. Siksi sokeriaineenvaihduntaa tutkitaan ja seurataan aina, jos herää pienikin epäily kehittymässä olevasta diabeteksesta.

Sattumalta esimerkiksi infektion yhteydessä todettu lievästi koholla oleva verensokeritaso on useimmiten vain elimistön stressi-hormonivasteen ylilyönti, mutta se voi myös olla ensimmäinen merkki hiipumassa olevasta insuliinituotannosta. Tämän takia

1. varmistetaan aina, että verensokeritaso palaa normaaliksi seuraamalla alkuun sokeriarvoja osastolla.
2. lapselle voidaan tarvittaessa antaa kotiin lainaksi verensokerimittari, jonka avulla seurataan verensokeritasoja.
3. kun lapsi on taas terve, tehdään vielä sokerirasituskoe, ja tarkistetaan, löytyykö verinäytteestä diabetekseen liittyviä autovasta-aineita.

Verensokerin kotiseurantaohjeet:

MITTAUS	KUINKA USEIN		MILLOIN YHTEYS LASTENKLINIKALLE
Paastoverensokeri	_____ kertaa viikossa	**Jos >7 mmol/l,** mitataan verensokeri 1 vrk ajan ennen kaikkia aterioita ja seuraavana aamuna	**Jos paastoverensokeri 2 kertaa >7 mmol/l tai mikä tahansa sokeriarvo >11 mmol/l** Lasten pkl: puh. 02-313 1420 Os. UB5: puh. 02-313 1418
Verensokeri 1.5-2 tuntia aterian jälkeen	_____ kertaa viikossa		
Jos runsasta juomista ja virtsaamista	Aina		

BLOOD GLUCOSE MONITORING
Tampere Clinical Center

NAME:
SSN:

DIPP-STUDY

Normal range:

Fasting blood glucose (the first BG measurement of the day)		3.5-6.1	mmol/l
Post-meal blood glucose 1-2 h after meal	below	7.8	mmol/l

DATE	Fasting blood glucose		Pre-meal BG		Post-meal BG	
	Time	Value:	Time	Value:	Time	Value:
	Time	Value:	Time	Value:	Time	Value:
	Time	Value:	Time	Value:	Time	Value:
DATE	Fasting blood glucose		Pre-meal BG		Post-meal BG	
	Time	Value:	Time	Value:	Time	Value:
	Time	Value:	Time	Value:	Time	Value:
	Time	Value:	Time	Value:	Time	Value:
DATE	Fasting blood glucose		Pre-meal BG		Post-meal BG	
	Time	Value:	Time	Value:	Time	Value:
	Time	Value:	Time	Value:	Time	Value:
	Time	Value:	Time	Value:	Time	Value:
DATE	Fasting blood glucose				Post-meal BG	
	Time	Value:	Time	Value:	Time	Value:
	Time	Value:	Time	Value:	Time	Value:
	Time	Value:	Time	Value:	Time	Value:
DATE	Fasting blood glucose		Pre-meal BG		Post-meal BG	
	Time	Value:	Time	Value:	Time	Value:
	Time	Value:	Time	Value:	Time	Value:
	Time	Value:	Time	Value:	Time	Value:
DATE	Fasting blood glucose		Pre-meal BG		Post-meal BG	
	Time	Value:	Time	Value:	Time	Value:
	Time	Value:	Time	Value:	Time	Value:
	Time	Value:	Time	Value:	Time	Value:
DATE	Fasting blood glucose		Pre-meal BG		Post-meal BG	
	Time	Value:	Time	Value:	Time	Value:
	Time	Value:	Time	Value:	Time	Value:
	Time	Value:	Time	Value:	Time	Value:
DATE	Fasting blood glucose		Pre-meal BG		Post-meal BG	
	Time	Value:	Time	Value:	Time	Value:
	Time	Value:	Time	Value:	Time	Value:
	Time	Value:	Time	Value:	Time	Value:
DATE	Paastoarvo		Pre-meal BG		Post-meal BG	
	Time	Value:	Time	Value:	Time	Value:
	Time	Value:	Time	Value:	Time	Value:
	Time	Value:	Time	Value:	Time	Value:
DATE	Fasting blood glucose		Pre-meal BG		Post-meal BG	
	Time	Value:	Time	Value:	Time	Value:
	Time	Value:	Time	Value:	Time	Value:
	Time	Value:	Time	Value:	Time	Value:
DATE	Fasting blood glucose		Pre-meal BG		Post-meal BG	
	Time	Arvo:	Time	Value:	Time	Value:
	Time	Arvo:	Time	Value:	Time	Value:
	Time	Arvo:	Time	Value:	Time	Value:

NOTE
If blood glucose level is below the normal range, warm up the child's hands and remeasure
If necessary, give some juice to the child
Please, contact the study doctor or study nurse if fasting blood glucose is over 7 mmol/l or if the blood glucose level measured at any time is over 11 mmo/l.

VERENSOKERISEURANTA

Tampere, Finland

DIPP -tutkimus

NIMI ____________________

SOTU ____________________

Normaalialue:

Paastoarvo (eli vrk:n ensim. Vs) 3,5 - 6,1

n. 1-2 tuntia ateriasta alle 7,8

PVM	Paastoarvo				Vs. arvo ennen ateriaa				Vs. arvo jälkeen aterian			
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
PVM	Paastoarvo				Vs. arvo ennen ateriaa				Vs. arvo jälkeen aterian			
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
PVM	Paastoarvo				Vs. arvo ennen ateriaa				Vs. arvo jälkeen aterian			
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
PVM	Paastoarvo				Vs. arvo ennen ateriaa				Vs. arvo jälkeen aterian			
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
PVM	Paastoarvo				Vs. arvo ennen ateriaa				Vs. arvo jälkeen aterian			
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
PVM	Paastoarvo				Vs. arvo ennen ateriaa				Vs. arvo jälkeen aterian			
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
PVM	Paastoarvo				Vs. arvo ennen ateriaa				Vs. arvo jälkeen aterian			
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
PVM	Paastoarvo				Vs. arvo ennen ateriaa				Vs. arvo jälkeen aterian			
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
PVM	Paastoarvo				Vs. arvo ennen ateriaa				Vs. arvo jälkeen aterian			
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
PVM	Paastoarvo				Vs. arvo ennen ateriaa				Vs. arvo jälkeen aterian			
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
PVM	Paastoarvo				Vs. arvo ennen ateriaa				Vs. arvo jälkeen aterian			
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	
	Klo.		Arvo:		Klo.		Arvo:		Klo.		Arvo:	

HUOM!

Jos verensokeri on normaalirajojen alapuolella lämmitä lapsen kädet ja kontrolloi tulos!
Tarvittaessa anna lapselle mehu tms.
Jos paastoverensokeri on yli 7mmol/l tai verensokeri koska tahansa mitattuna suurempi kuin 11 mmol/l, niin ota yhteys tutkimuslääkäriin tai hoitajiin.

Oulu Clinical Center

Week/Year	BREAKFAST Before	After	LUNCH Before	After	SNACK Before	After	DINNER Before	After	EVENING SNACK Before	After	MORE INFROMATION e.g. exercise, illness, delicacies and candies	
Date/ BG												
Date/ BG												
Date/ BG												
Date/ BG												
Date/ BG												
Date/ BG												
Date/ BG												
Date/ BG												
Date/ BG												

Please, contact the type 1 diabetes research center during the business hours tel. 050-4087109/08-31505147

if fasting blood glucose (BG) level is ≥ 7 mmol/l or post-meal value (1.5 h or 2 h after the meal) is > **11.0 mmol/l.**

Outside of business hours, please contact the child emergency duty service at Oulu University Hospital tel. 08-315 5260

Vko/vuosi		AAMUPALA ennen	AAMUPALA jälkeen (1.5-2h)	LOUNAS ennen	LOUNAS jälkeen (1.5-2h)	VÄLIPALA ennen	VÄLIPALA jälkeen (1.5-2h)	PÄIVÄLLINEN ennen	PÄIVÄLLINEN jälkeen (1.5-2h)	ILTAPALA ennen	ILTAPALA jälkeen (1.5-2h)	LISÄTIETOJA esim. liikunta, sairastelut, herkut ja karkit
Pvm	Vs											
Pvm	Vs											
Pvm	Vs											
Pvm	Vs											
Pvm	Vs											
Pvm	Vs											
Pvm	Vs											
Pvm	Vs											
Pvm	Vs											

MIKÄLI VERENSOKERIN PAASTOARVO ≥ 7
TAI ATERIANJÄLKEINEN VERENSOKERI (1.5-2h aterian jälkeen) ≥11.0
NIIN YHTEYS VIRKA-AIKAAN DIABETESTUTKIMUKSEEN P. 050-408 7109 / 08-315 5147
TAI VIRKA-AJAN ULKOPUOLELLA YHTEYS OYS:N LASTEN PÄIVYSTYKSEEN P.08-315 5260

M4. Home Glucose Testing Instructions – Georgia

IMPORTANT SAFETY INSTRUCTIONS:

- This meter and lancing device are for single patient use only. **Do Not** share them with anyone else, including family members! **Do Not** use on multiple patients!
- After use and exposure to blood, all parts of this kit are considered biohazardous. A used kit may potentially transmit infectious diseases even after you have performed cleaning and disinfection.

For more information see: FDA Public Health Notification: "Use of Fingerstick Devices on More than One Person Poses Risk for Transmitting Bloodborne Pathogens: Initial Communication" (2010) http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm224025.htm.

CDC Clinical Reminder: "Use of Fingerstick Devices on More than One Person Poses Risk for Transmitting Bloodborne Pathogens" (2010) http://www.cdc.gov/injectionsafety/Fingerstick-DevicesBGM.html.

Refer to your User Guide or Owner's Booklet for important information about cleaning and disinfecting your meter, lancing device, and caps.

Intended use

The OneTouch® Verio® Blood Glucose Monitoring System is intended to be used for the quantitative measurement of glucose (sugar) in fresh capillary whole blood samples drawn from the fingertip. The system is intended to be used by a single patient and should not be shared.

The OneTouch® Verio® Blood Glucose Monitoring System is intended for self-testing outside the body (*in vitro* diagnostic use) by people with diabetes at home as an aid to monitor the effectiveness of diabetes control.

The OneTouch® Verio® Blood Glucose Monitoring System is not to be used for the diagnosis of or screening of diabetes or for neonatal use. The OneTouch® Verio® Blood Glucose Monitoring System is not for use on critically ill patients, patients in shock, dehydrated patients or hyperosmolar patients.

Get to know your system

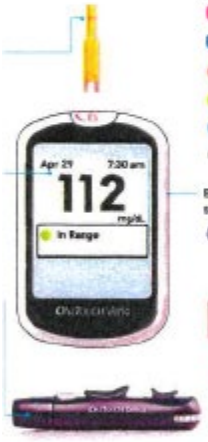
OneTouch® Verio® Test Strip
Side filled design lets you apply a drop of blood to either side of the test strip.
It's the only test strip that works with your OneTouch® Verio® Meter.

OneTouch® Verio® Meter
Large display makes it easy to see your results.
Color-coded range indicator helps you understand your results.
Side buttons make it easy to use.

OneTouch® Delica® Lancing Device
Designed for comfortable testing.

See Owner's Booklet for additional details.

As your partner in diabetes care, we welcome you to contact us (7 days a week, 8 a.m. - 10 p.m. Eastern Time) at 1 888 567-3003 (English), 1 888 567-3010 (Español), or www.OneTouch.com.



Symbols on the display

- High Pattern
- Low Pattern
- Above Range
- In Range
- Below Range
- Control solution

Buttons on the side

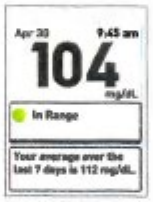
- Press and hold to turn meter on/off; press and release to confirm a selection
- Scroll up through screen entries
  Scroll down through screen entries
- Press and release to go back; press and hold to go to Main Menu

Get started testing

Insert a test strip and wait for the **Apply Blood** screen to appear.

Get a drop of blood and apply it to either side of the test strip.

Wait for the meter to count down and display your glucose test result.

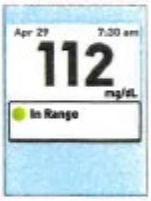


Messages will automatically appear to help you understand your results.

Your **7 Day Average** shows up automatically when you test two or more times over the past 7 days.

Quick Tips: In Range results

- 4 types of **In Range** messages tell you when you are on the right track.
  - **In Range** message
  - **In Range** / 7 Day Average message
  - 2 types of Progress Notes: Achievement and Consistency
- Identify the things that are working and continue these good habits.
- Consider how your eating habits – foods, portions or schedule – affect your ability to stay **In Range**.
- Consider how physical activity levels impact your glucose levels.



CENTER FOR BIOTECHNOLOGY & GENOMIC MEDICINE

Jennifer Bryant, RN, BSN
TEDDY Research Manager

jbryant@augusta.edu

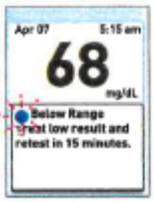
Mailing Address:
6105 Peachtree Dunwoody Road
Building A, Suite 215
Atlanta, Georgia 30328

Direct (770) 837-3809 **Fax** (770) 837-3702 **Cell** (770) 365-7069

cbgm.augusta.edu
augusta.edu

Quick Tips: Low & High results

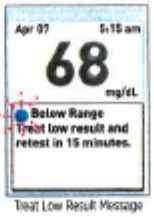
- **Below Range** messages tell you when you are below your low range limit. Low Pattern messages let you know if this is happening consistently.
- Could a change in your eating habits (e.g., skipped meal) or an increase in activity be the cause?



- **Above Range** messages tell you when you are above your high range limit. High Pattern messages let you know if this is happening consistently.
- Could a change in your eating habits (e.g., too many carbs) or reduced activity be the cause?

Know if you are in range or out of range

Above Range
In Range
Below Range



Treat Low Result Message

A color dot and message appear below your result to let you know if you're within, below or above your range limits.

The range limits are the ones you set in the meter.

When your result is below the low range limit, your meter will prompt you to treat and retest.

Know when you're making progress

Consistency Message

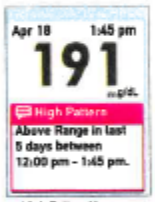
Achievement Message

A **Consistency Message** tells you how often your past several results have been in range during the past 7 days.

An **Achievement Message** tells you when your current result is in range following three or more results in a row that were above your high range limit.

NOTE: The **Progress Note** (Consistency and Achievement) message must be turned on for these messages to be displayed.

Know when you've developed a pattern



High Pattern Message

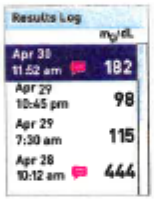
Low Pattern Message

High Pattern messages tell you when your results are consistently above your high range limit around the same time of day.

Low Pattern messages tell you when your results are consistently below your low range limit around the same time of day.

NOTE: Pattern messages must be turned on for these messages to be displayed.

Know your glucose history



Review your individual glucose results on the **Results Log** screen.

Check your glucose averages over several time periods on the **Averages** screen.

Manufactured by:
LifeScan Europe
Division of Cilag
GmbH International
Gubelstrasse 34
6300 Zug
Switzerland

Made in China

Rev. Date: 02/2014
Patented.
© 2014 LifeScan, Inc.

The OneTouch® Verio® System

Get more information automatically*

*More than just a number

AW 06908801A

CENTER FOR BIOTECHNOLOGY & GENOMIC MEDICINE

Jennifer Bryant, RN, BSN
TEDDY Research Manager

jbryant@augusta.edu

Mailing Address:
6105 Peachtree Dunwoody Road
Building A, Suite 215
Atlanta, Georgia 30328

Direct (770) 837-3809 Fax (770) 837-3782 Cell (770) 365-7069

cbgm.augusta.edu
augusta.edu

14. Laboratory Measurements

PLEASE follow the Sample Processing Procedures specifically as given below, to ensure sample quality across sites!

14.1. Blood Samples

14.1.1. Serum – SST Tube

Serum Processing

a. Allow to clot for at least 30 minutes in a vertical position. If fibrin clumps occur in the centrifuged serum, increase the clotting time to 45 minutes before centrifugation.
b. Centrifuge at room temperature at full speed (between 1100 and 1300g) for 10 minutes for a swinging head unit or 15 minutes for a fixed angle unit (balance tube in centrifuge). The serum will be separated from clot by the gel barrier.
c. Transfer serum by pipette into etched TEDDY cryovials and cap.

Serum aliquoting – 3 – 33 month clinic visits

a. 0.2 ml of serum into a 0.5 ml cryovial with a red insert for autoantibodies for the reference lab
b. 0.2 ml of serum into a 0.5 ml cryovial with a red insert for autoantibodies for the repository and confirmation testing.
c. 0.1 ml of serum into a 0.5 cryovial with a yellow insert for serum cytokines/inflammation markers.
d. Any additional serum into a 2.0 ml cryovial with a gray insert for storage at the repository.

Serum aliquoting – 36 month – 15 year clinic visits

a. 0.2 ml of serum into a 0.5 ml cryovial with a red insert for autoantibodies for the reference lab.
b. 0.2 ml of serum into a 0.5 ml cryovial with a red insert for autoantibodies for the repository and confirmation testing.
c. 0.1 ml of serum into a 0.5 cryovial with a yellow insert for serum cytokines/inflammation markers.
d. 0.1 mL of serum into a 0.5 mL cryovial with a green cap insert for additional serum aliquot tube 1.
e. 0.1 mL of serum into a 0.5 mL cryovial with a green cap insert for additional serum aliquot tube 2.
f. Any additional serum should be aliquoted according to the following specifications into a 2.0 ml cryovial with a gray insert for storage at the repository:

Aliquoting schedule for all subjects:

i. 0.5 ml should be aliquoted into each of the first two storage tubes

ii. Then 1.0 ml should be aliquoted into the next three storage tubes
iii. Then 1.5 ml should be aliquoted into the next five storage tubes
iv. If there is not enough serum to make a 0.5 ml aliquot or 1.0 ml aliquot, the minimum volume to aliquot into a tube is 0.1 ml. If there is not at least 0.1 ml left, then the remaining serum should be added to the last aliquoted tube and the sample volume should be accurately recorded on the SCF.
    1. For example: If a total of 3.6 ml of serum is collected for storage, the first 1.5 ml will be aliquoted into three 0.5 ml aliquots, then 1.8 ml will be aliquoted into the next storage tube and then 0.3 ml in the fifth storage tube.
        a. NOTE: If the remainder was less than 0.1 ml, the remainder would be added to the 0.5 ml in the third tube.
v. This aliquoting scheme will yield a maximum of 10 serum storage tubes holding a maximum total volume of 11.5 ml. If any excess, add to the last 1.5 ml storage tube.

Additional volume at 24 month visit and then annually for tissue transglutaminase antibodies

a. Additional 0.02 ml for tissue transglutaminase antibodies measurement added to the islet antibody sample sent to the Autoantibody Reference Lab
    i. If the annual transglutaminase antibodies sample, which starts at 2-years, is positive, the antibodies are analyzed again after 3 months, so an additional 0.02 ml for tissue transglutaminase antibodies measurement will be added to the islet antibody sample sent to the Autoantibody Reference Lab; if negative the antibodies are analyzed again after one year. If confirmed positive, the child will have attained the TEDDY study endpoint for transglutaminase antibodies. Children positive and those negative for transglutaminase antibodies will continue to be screened annually.

Additional volume at 8 year visit and 14 year visit for Thyroid testing

a. Aliquot 0.1 ml of serum into a 0.5 mL cryovial with a blue cap insert for the Thyroid Autoantibody sample at the 8 year visit (or current visit for those older than age 8 when Thyroid testing was added to the protocol or for subjects who have been inactive or dropped out and rejoined) and the 14 year visit. Thyroid peroxidase (TPOA) and thyroglobulin (ThGA) will be tested on these samples. Samples from children positive for either thyroid antibody will also be tested for TSH in the same sample.

NOTE: these samples must be shipped to the Thyroid lab within 2 weeks of collection as TSH is only stable for 1 month.

i. The thyroid sample should be aliquoted after the autoantibody reference lab and autoantibody repository sample (red cap inserts).

ii. Children positive for TPOA and/or ThGA at the 8 year visit and/or the 14 year visit will have a confirmatory sample draw at the next TEDDY visit, which will be analysed for TPOA and ThGA. Sites should aliquot 0.025 mL of serum into a 0.5 mL cryovial with a blue cap insert to be used for TPOA and ThGA confirmatory testing.

iii. If the 8 year or 14 year Thyroid sample is positive for either TPOA or ThGA and is unable to have TSH run on it due to low volume, we have programmed our system to have TSH run on the confirmatory sample.

a. The site should collect extra serum for the confirmatory sample so that TSH can be run on it - the site should aliquot 0.1 ml of serum into a 0.5 mL cryovial with a blue cap insert. There will be a message in red at the top of the Thyroid confirmatory SCF that alerts the site to aliquot extra serum for the confirmatory sample. Also the site will receive an automatic email notification when the lab uploads the low volume sample status code for the 8 year or 14 year TSH results letting them know that TSH was unable to be run on the 8 year or 14 year sample due to low volume.

Maternal sample serum aliquoting – to be collected only if mother has type 1 or 2 diabetes or gestational diabetes and/or child is shown to be autoantibody positive at 3 or 6 months of age. This sample is only collected from the mother one time during the study and can be collected up to the 24 month visit

a. 0.1 ml of serum into a 0.5 ml cryovial with a red insert for maternal autoantibodies for the reference lab
b. 0.1 ml of serum into a 0.5 ml cryovial with a red insert for maternal autoantibodies for the repository and confirmation testing.
c. Any additional serum into a 2.0 ml cryovial with a gray insert for storage at the repository.

Serum Storage

Enter each Serum sample's information onto the Sample Collection Forms (see Section 14.1.7.) then store Serum samples at -70 °C, within 2 hours after processing, until shipping.

14.1.2. Plasma, PBMC, Buffy Coat, and Erythrocytes – CPT Tube

CPT Tube Processing

Plasma samples collected for annual visits should be protected from light exposure. CPT tubes should be foil wrapped and plasma should be continuously protected from light throughout processing until the portions requiring aliquoting into amber cryovials are completed.

a. After collection, store CPT tube upright at room temperature for not more than two hours.
b. Before centrifugation, remix by gently inverting the tube 8-10 times. **NOTE: THIS STEP IS VERY IMPORTANT.**
c. Using a centrifuge with a swing-out rotor, centrifuge the tube with blood sample at 1800 X g RCF for 20 minutes at room temperature.

Plasma aliquoting

a. Using pasteur pipette, harvest 2/3 of the upper (plasma) layer.
b. First pool the plasma from up to three 8 ml CPT tubes into one 15 ml sterile Sarstedt (15ml) tube (same as used also for PBMC) and then aliquot plasma into cryotubes using per-tube volumes specified in the MOO instructions.
c. Store the ascorbic acid sample in trichloride acetic acid.
d. Collect the lymphocyte/monocyte layer (between the plasma layer and the gel barrier density fluid) and transfer from the CPT tube into a 2 ml cryovial. You should have a volume of approximately 0.5 ml.

NOTE: PROCEED WITH CERTIFICATION ACCORDING TO POWERPOINT FILE ENTITLED "TEDDY PBMC CERTIFICATION PROCEDURES". ONCE CERTIFIED, PLEASE BEGIN ROUTINE TEDDY PBMC ISOLATION.

Isolation and Cryopreservation of PBMC from CPT tube with prior plasma harvest

PBMC preparation should be completed EXACTLY as this protocol specifies.

Although many technicians are skilled in PBMC cryopreservation, TEDDY requires a standardized procedure across all TEDDY sites. TEDDY PBMC certification is required to familiarize laboratory technicians with the TEDDY PBMC protocol and to ensure that all TEDDY specimens are of the highest quality possible. Anyone who will be isolating PBMCs for the TEDDY study must complete and pass TEDDY PBMC certification. Please see details of certification process in PowerPoint file entitled "TEDDY PBMC Certification Procedures".

It is expected that each Clinical Center will be able to isolate and freeze sterile PBMC from 8 or more TEDDY subjects per day. Occasionally, the available samples will exceed the local capacity to process them, in which case the following priority order will be used:

1) first degree relatives;
2) general population subjects who are Genotype Category A (HLA DR3/4);
3) general population subjects who were positive for any islet autoantibody at the last TEDDY visit;
4) all other general population subjects.

Purpose: To isolate and freeze sterile viable PBMC from fresh whole blood samples obtained in the TEDDY follow-up protocol, while maintaining the harvest of sera and RBC membranes per pre-existing TEDDY goals. This protocol merges the IDS "cold protocol" (*IDS-TCW Fresh-Frozen SOP 1.3)* and ITN CPT protocol (PBMC CPT v.009).

Materials:

Sterile 50 ml polypropylene tubes
Sterile 15 ml polypropylene tubes
RPMI 1640 medium sterile, room temperature
Freezing solution A (100% human AB serum) and B (80% human AB serum + 20% DMSO) - 1 set = one 5 ml tube of solution A and three 1.8 ml tubes of solution B
10 ml serological pipettes
Wide bore sterile Pasteur or bulb pipettes
2 ml etched cryovials
Thermo Scientific Nalgene "Mr. Frosty" Freezing Container – keep ready for use, filled with isopropanol, at 4°C or a pre-chilled CoolCell (4˚C); you need one Mr. Frosty per 6 TEDDY individuals drawn or one CoolCell per 4 TEDDY subjects and it takes at least 4 h to re-cycle a -80˚C unit to 4˚C so plan ahead.

> To rapidly recycle CoolCell to room temperature, remove the center solid core ring. CoolCell body and lid will return to room temperature in 10 to 15 minutes. Check that all chambers are dry. Dry the core ring before re-inserting into the central chamber. The 12 chambers and cryovials should be dry to avoid tube sticking upon freezing. Place the CoolCell in the refrigerator (+4˚C) for at least 4h before loading with cell suspensions.

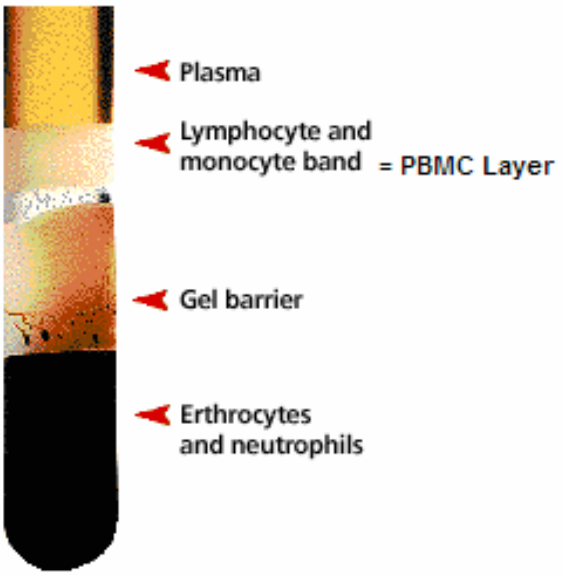
Trypan blue vital dye (liquid suspension)
Neubauer hemocytometer

The procedure should be completed, from first spin through placement of cell aliquots placed in Mr. Frosty or CoolCell and then placed in -80°C freezer, within 3 hours, with the time between any individual steps not exceeding 15 minutes.

Initial Steps

P1. Obtain blood by venipuncture into CPT tubes, gently but fully invert 5 times to mix, DO NOT SHAKE. Follow TEDDY volume guidelines for minimum CPT volumes to ensure functioning of CPT density gradient. This is at least 3 ml blood for a 4 ml CPT tube and at least 6 ml blood for an 8 ml CPT tube. Store the tube upright until processing. The CPT tube should be processed within 2 hours of blood draw. Before centrifugation, remix the blood by gently inverting the tube 8-10 times. Spin at 18-25°C at 1500g-1800g RCF for at least 20 min. Keep the brake OFF. Note: Use a centrifuge with horizontal rotor (swinging bucket) and an adaptor that can accommodate a 16x125 mm size tube.

After centrifugation you should be able to see the described layers:



P2. Place freezing media on ice. Note lot numbers of media in the provided field on the Plasma SCF (underneath the "PBMC Tube #1" test name field). Sites should enter the lot number for both solution A and solution B. If solution A and B come from the same lot number, the lot number should be entered in both fields.

P3. Under sterile technique in laminar flow hood using a sterile pipette, harvest the plasma (top) layer to within 1 cm of the cell layer into separate sterile container for aliquoting per TEDDY guidelines. Working slowly and using side illumination to aid in visalization of cells, harvest additional plasma to within 0.5 cm of cell layer, taking care not to remove any cells. Use sterile technique in a laminar flow hood at all times.

P4. Mix the cells with the remaining plasma by gentle pipetting with a plastic Pasteur pipette and transfer the cells into a sterile 15 ml polypropylene tube. Wash the CPT tube with 2 ml of RPMI by gentle pipetting and transfer the cells into the same 15 ml tube. Fill tube with 12ml RPMI, balance tubes, and centrifuge at 300g for 10 min at 16-25°C.

P5. Remove supernatant carefully with 10ml pipette taking care not to disturb the pellet, (DO NOT POUR OFF). The pellet should be white with no red blood cell contamination.

P6. Loosen the pellet by tapping the tube with your finger. Then resuspend the pellet gently in fresh RPMI using a 10ml pipette. Centrifuge again at 200g for 10 min at room temperature.

P7. Remove supernatant carefully with 10ml pipette taking care not to disturb the pellet (DO NOT POUR OFF). Resuspend cells gently in RPMI. To aid in accurate counting, volume of media added should allow for a final concentration of one to four million cells per ml.

P8. Label all cyrovials with subject ID. Aliquot according to table below. Place cryovials on ice. Cells are frozen at a final concentration of 10 x 10^6/ml.

Millions of cells isolated total	Final volume ml/cryovial	# of 2 ml cryovials (no cap insert)
3 to <5	0.30 to 0.50	1
5 to <9	0.25 to 0.45	2
9 to <16	0.30 to 0.53	3
16 to <20	0.40 to 0.50	4
20 to <25	0.40 to 0.50	5
25 to 30+	0.41 to 0.50+	6

Note that for certification only, PBMC from each subject should be aliquoted into only ONE cryovial to facilitate core lab analysis.

P9. Count PBMC using the protocol shown below.

Counting Cells

CNT1. To prepare the Neubauer hemocytometer, first clean the hemocytometer with H2O and then with 70% ethanol. Dry it off with a Kimwipe.

CNT2. To get an equal cell distribution, mix cell suspension prior to adding the stain and again just before loading the Neubauer hemocytometer.

CNT3. Stain cells with Trypan Blue: On a piece of parafilm (parafilm can be replaced by Eppendorf tube or well from 96-well plate) combine 20 µl of cell suspension that was set aside in P7 with 20 µl of 0.4% Trypan Blue (1:1). Use equal volumes of stain and cells! Mix well with pipette. Note: After mixing cells with Trypan Blue, count cells immediately. Your goal is to achieve an accurate cell distribution with cell clumping kept to a minimum.

CNT4. Center a cover glass over the hemocytometer chambers, attaching with THIN layer of water. Do not use excess water.

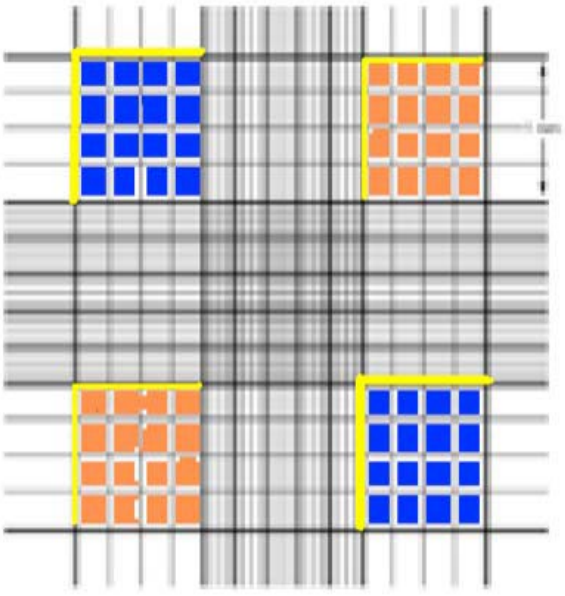
CNT5. Fill one chamber (V-groove) with 10 µl of the cell dilution using a 20 µl pipette. The solution will pass under the cover glass by capillary action. Do not over-fill. Allow the cell suspension to settle in the hemocytometer for at least

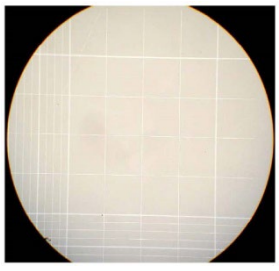
10 seconds before counting. If the solution spreads into the 2 lateral grooves adjoining the grid table, clean the hemocytometer and repeat the application. If there are any bubbles in the solution covering the grid table clean the hemocytometer and repeat the application. Place the hemocytometer on the stage of a microscope, adjust focus using 10X objective, then change to 20X and refocus if necessary.

CNT6. Assess if the cells are evenly distributed among the squares. Also, PBMCs may contain population of erythrocytes which look different from PBMC. Use caution when counting cells to distinguish lymphocytes from erythrocytes.

CNT7. Count live cells (non-blue) in the 4 large corner squares of the Neubauer Hemocytometer. Squares are represented in the image below left as blue and orange. The below right image is an actual view of the counting grid. Include cells that touch either the top line or left vertical perimeter line of any corner square (indicated with yellow lines). Do not count any cells that touch either the bottom line or right vertical perimeter line of any corner square. Determine the number of cells per ml using the formula:
Viable cells/ml= (total # of viable cells in all 16 subsections of 1 orange square) x 10^4 x dilution factor. The dilution factor is 2 if you mixed trypan blue dye with cells in a 1:1 ratio.
Then calculate the total number of viable cells as:
Total viable cells = viable cells/ml x volume of original cell suspension

Blue cells are dead, and clear cells are alive. Count live and dead cells and record the results separately (note: The image on the right featuring 16 subsections is a magnified view of one of the squares represented in either blue or orange from the left hand image).





Freezing Cells

CF1 Spin cells (please see details below), remove most of the supernatant carefully by pipette, loosen the cell pellet by gentle tapping, add the appropriate amount of ice cold Freezing Medium A to adjust the cell concentration to 20 million/ml. Mix cells by gently tapping the tube; do not use a pipette. Ensure cells are in a single cell suspension.

Temperature: 4˚C
RPM's: 1200
G's: 298
Time: 5 minutes

CF2 Slowly, drop by drop, add to the side of the tube an equal volume of Freezing Medium B (20%DMSO) to Freezing Medium A containing the PBMCs using a wide bore Pasteur Pipette, mix the cells by a gentle continual swirling motion during the addition to ensure steady mixing of the two freezing solutions. This step should take 2 minutes. GENTLY pipette up and down 3 times using a serological pipette. Avoid bubbles. The final concentration should be 10 million/ml. Once mixing is complete, aliquot appropriate volume of PBMC suspension per cryovial on ice (note 1 ml = 10 million PBMC).

CF3 Once mixing is complete, aliquot appropriate volume of PBMC suspension per cryovial on ice (note 1ml= 10 million PBMC).

Cells are frozen at a final concentration of 10 x 10^6/ml.

Millions of cells isolated total	Final volume ml/cryovial	# of 2 ml cryovials (no cap insert)
3 to <5	0.30 to 0.50	1
5 to <9	0.25 to 0.45	2
9 to <16	0.30 to 0.53	3
16 to <20	0.40 to 0.50	4
20 to <25	0.40 to 0.50	5
25 to 30+	0.41 to 0.50+	6

Note that for certification only, PBMC from each subject should be aliquoted into only ONE cryovial to facilitate core lab analysis.

CF4 Place the cryovials into a Nalgene Cryofreezing Container ("Mr. Frosty") or into a Biocision CoolCell. Mr. Frosty should be at 4°C and should be pre-filled to prescribed line with isopropanol. The CoolCell should be at 4˚C and should be completely dry. Immediately place either freezing container into -80°C freezer for at least two days. During the freezing time avoid opening the freezer in order to avoid shaking the cryovials or raising the freezer's temperature. Then remove cryovials and store in a separate freezer box inside of a Styrofoam shipper box inside a -80˚C freezer. We recommend using a 2" freezer box with 81 cell divider insert and a Styrofoam Saf-T-Pak STP-309 shipper box or equivalent. Always use dry ice to transfer cryovials containing cells to permanent

storage or when you check barcodes against shipping lists before shipment to Repository to avoid temperature rise and cell damage. Cryovials contents can rise from -80˚C to over -50˚C in less than one minute if exposed to room temperature air. It is not necessary to use the Styrofoam lid during -80°C storage. PBMC samples should then be shipped to the Repository every 2 weeks for US sites and European sites should ship in bulk shipments with their monthly Repository shipments (due to high shipping costs). PBMC samples should be shipped to the Repository in separate freezer boxes from the other samples being shipped to the Repository and should be labeled "PBMCs" if the samples are being shipped to the Repository in the same shipping box as other samples- upon receipt the Repository will store the samples in liquid nitrogen long-term. Please note that the Clinical Centers should NOT place the samples in liquid nitrogen before shipping the samples to the Repository.

Data Submission

For ALL PBMC isolations, please record and submit the date and time of the blood draw, the date and time of the PBMC processing and the total volume of whole blood added to all the CPT tubes from that draw. Please also record and submit the volume and concentration of cells placed into each individual cryovial from that draw. See MOO section 14.1.7. for details.

PBMC QC Samples

1. Every six months TEDDY Clinical Centers that collect PBMC samples for TEDDY should collect PBMC samples from two non-TEDDY subjects for QC purposes. One of these should be processed within 6 hours of collection and the other processed between 16 and 24 hours of collection.
2. Sites should follow the same collection and processing procedures as they do for regularly collected TEDDY PBMC Samples as outlined in this Manual of Operations (see MOO section 14.1.2. for details)
3. Enter information on PBMC QC SCF:
   a. Logon to the TEDDY website http://teddy.epi.usf.edu/
   b. Click on "Quality Control Samples" link under "Data Management" on the left navigational toolbar.
   c. Choose SCF entitled "PBMC Samples". (If you would like to view a Quality Control SCF that has already been submitted you can either enter 1) Sample Code & Sample ID and select 'search' – see letter s for explanation of these - or 2) select your clinical center and visit location code from the drop down menus and select 'search'.)
   d. Choose the visit location code.
   e. Enter the Date of Collection (DD/MMM/YYYY)
   f. Enter the time the sample was drawn.
   g. Enter the date the sample was processed.

h. Enter the time the sample was processed (this is the time the sample was put in the freezer).
i. Enter the estimated total blood volume (within approximately 1 mL) of whole blood added to all CPT tubes from this draw used for PBMC isolation, prior to processing. This is the amount of whole blood added from syringe, not the final volume including reagent in the tube. If you drew directly into the CPT tube, use a calibrated tube to measure volume of whole blood added.
j. Find the row containing the "Test Name" (i.e. PBMC QC tube #1, PBMC QC tube #2, PBMC QC tube #3) of the sample in the vial you would like to scan. If there is an insufficient volume, check the "Insufficient Volume" Box in the appropriate row, repeat this step as necessary then continue to letter r; if there is a sufficient amount go to letter k.
k. For the first PBMC vial enter the lot number of the freezing media serum.
l. Place cursor in the "Vial Barcode Number" box in this row.
m. Scan the preprinted barcode located on the cryovial containing this particular sample.
n. In the provided spaces enter the volume and cell count.
o. In the provided space enter box number and space number where the sample will be stored.
p. Place the cryovial in the exact freezer box and space number that you entered on the SCF for that particular sample.
q. Repeat steps l-p as necessary.
r. When all samples for this specific SCF have been entered, click the "Save Form" button at the top of this form.
s. Once the form has been saved the samples entered on the SCF will be assigned to one 'Sample ID' and one 'Sample Code' (which you can use to search for these samples if necessary - see letter c).

4. Store PBMC samples at –70°C to -80°C; send to the Repository on dry ice every two weeks with regular TEDDY PBMC samples

Processing of mononuclear cells (buffy coat) using CPT tube

For subjects where it is not possible to isolate and freeze living PBMC, the cells will be harvested and frozen as a buffy coat sample. This collection requires a whole blood sample of 2 ml or more added to the Becton Dickinson CPT tube at room temperature, using standard technique for Vacutainer tubes directly or via syringe.

a. Add 1.5 ml of PBS (phosphate buffered saline), recap tube, invert mix several times, and spin 5 minutes at 1800 x g RCF.
b. Shine a light source through the tube supernatant to inspect. After verifying that no cells remain in the supernatant, collect the supernatant by pipette and discard, leaving the white cell pellet in the bottom of the

tube (2 ml cryovial with **no** cap insert). Note that the size of the white cell pellet may vary from subject to subject.

c. Store tube at –70°C to -80°C immediately after processing

Erythrocyte Processing

These must only be processed at the 3, 6, 12 and then yearly clinic visits (from the 12 month visit onward).

After harvesting the plasma and buffy coat:

a. Insert a wooden stick or disposable lab spatula along the glass edge of the vacutainer until it penetrates the gel barrier.
b. Simultaneously push down on the gel and pull out the wooden stick, smearing the gel on the opposite side of the vacutainer.
c. Insert a disposable transfer pipette into the RBC, and withdraw a 1 ml sample (if possible).
   NOTE: It may be difficult going straight into and out of the tube to avoid the gel. If the pipette touches any gel going in, it will plug the opening. If the pipette touches any gel coming out, it will contaminate the sides making it difficult to transfer the RBC into the cryovial without also adding in gel.
d. Transfer Erythrocyte pellet into 12 ml round bottom polycarbonate tube for processing.
e. Process Erythrocytes*
   1. Resuspend the erythrocyte pellet by adding 5 ml 0.9% NaCl.
   2. Centrifuge the tube at 800 X g for 10 minutes. Discard the supernatant.
   3. Repeat previous steps 1 and 2 twice more.
   4. Add 1 ml distilled water to the final pellet.
   5. Add 2 ml 2-propanol supplemented with 50 mg/l butylated hydroxytoluene(BHT) drop by drop. Gently shaking the tube while you are adding the BHT solution to mix it.
   6. Transfer the erythrocyte solution from the round bottom polycarbonate tube into two 2.0 ml cryovials with blue inserts.

   *For volumes of RBC less than 0.5 ml:
   1. Follow steps 1, 2 and 3 as indicated above.
   2. Resuspend Red Blood Cells in 0.5ml distilled water.
   3. Add 2ml 2-propanol supplemented with 50 mg/l butylated hydroxytoluene(BHT) drop by drop.
   4. Transfer the erythrocyte solution from the round bottom polycarbonate tube into two 2.0 ml cryovials with blue inserts.
f. Store cryovials at –70°C to -80°C immediately after processing.

TEDDY Isolation of (A) PBMC by Ficoll Gradients or (B) Buffy Coat (CPT replacement)

Purpose: TEDDY isolation of citrated plasma and PBMC or buffy coat during time of CPT tube shortage

SOP A: PBMC Isolation

Supplies (for each PBMC prep):

- 30 ml Ficoll Paque Plus
- 2 fritted 50 ml Leucosep tubes
- 2 x 50 ml conical tubes
- 32 ml Hank's Balanced Salt Solution

(All steps in laminar flow hood using sterile technique and sterile tubes and pipettes)

a. Add 15 ml **Ficoll Paque Plus** under sterile technique to each of 2 fritted **50 ml Leucosep tubes**, spin 1000 x *g* for 2 min to bring liquid below frit. Can be prepared in advance, stored at 4°C, then brought to room temp on day of possible use, and refrigerated again if not used.

b. Use filled tubes drawn in clinic (9 x **2.7 ml sodium citrate Vacutainer tubes**, light blue top, NO serum separator). This is drawn instead of 3 x 8 ml into CPT tubes so that the same blood volume is drawn from the subject. In sterile hood, using serological pipette, pool the citrated blood into one 50 ml conical tube, cap, spin 10 min at 1500 × *g* at room temp.

c. **For Annual Visits** retain one foil-covered 2.7 ml sodium citrate tube, spin separately for red blood cell recovery*. Pool the blood from the remaining 8 x 2.7 ml sodium citrate tubes into one 50 ml conical tube, cap, spin 10 min at 1500 × *g* at room temp and continue with the protocol.

d. Into a separate sterile 10 ml tube, CAREFULLY harvest plasma supernatant from the 50 ml conical tube without disturbing the cell pellet. You should try to take one third of the total starting blood volume, which is ~8 ml if you started with 24 ml. This would leave ~4 ml of plasma above the cell pellet. The amount taken and amount left should be scaled proportionately if the starting blood volume is less. This plasma is saved and later distributed into TEDDY cryovials the same as in CPT protocol. See MOO Section 14.1.2 Page 15 for plasma aliquoting and storage.

e. To the 50 ml conical tube, use a 25 ml serological pipette to add sterile **Hanks Balanced Salt Solution (Ca++ and Mg++ free)**. Add a volume equal to the sum of the plasma volume removed PLUS the volume of the original pooled citrated blood. For example, if you started with 24 ml citrated blood, and after spin you removed 8 ml plasma, you should add 8 + 24 = 32 ml of Hanks solution to end up with 48 ml total volume. Mix gently by up and down by pipetting using a 25 ml serological pipette to ensure full suspension of the red cell pellet.

f. Apply half of the diluted blood from step d to each preloaded Leucosep tubes from step 1.

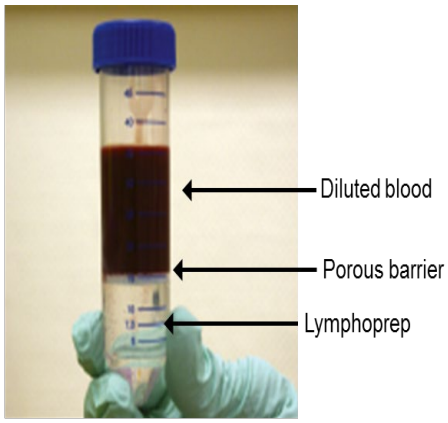


Figure 1. Diluted blood is added to the Leucosep tube.

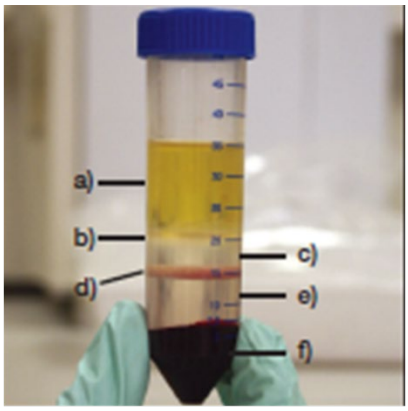


Figure 2. Leucosep tube after centrifugation. ***a***, Plasma; ***b***, PBMC/lymphocyte interphase; ***c***, separation medium; ***d***, porous barrier; ***e***, separation medium; ***f***, pellet (erythrocytes, granulocytes)

g. Centrifuge for 12 min at 1000 × *g* with brake OFF and centrifge at room temperature. When the centrifuge stops, remove Leucosep tubes and continue working inside laminar flow hood. Using serological pipette, aspirate and DISCARD the diluted plasma layer because it is too dilute. Leave a small amount of this liquid above the cell layer as in Figure 5.

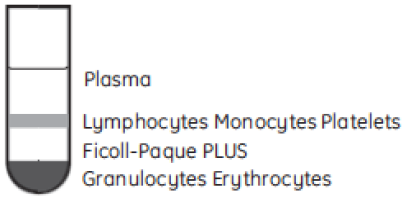


Fig 4.

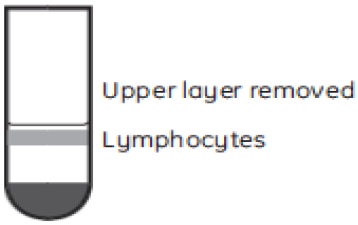


Fig 5.

h. Next, collect the mononuclear cells from the plasma/Ficoll interphase using a serological pipette, and place the cells into a new 50 ml conical tube. While collecting the cells, be sure to aspirate the residual plasma above the lymphocytes, but as little Ficoll below the lymphocytes as possible. Pool the interphase from the 2 large tubes into the one new 50 ml tube. This should be done with similar technique to that used in the past for CPT tubes.

i. Add sterile PBS (room temp) to bring the final volume in the tube to 50 ml. Then process cells the same as for CPT protocol.

j. To isoloate PBMCs from this point refer to MOO Section 14.1.2 Page 6

k. To isolate a white blood cell pellet refer to MOO Section 14.1.2 Page 11

Protocol specific Materials

Ficoll Paque Plus (Cytiva, 17-1440-02, Sigma-Aldrich)

50 ml sterile Leucosep tubes, cat # 227290, Greiner. Fisher cat # 07-000-983

2.7 ml sodium citrate Vacutainer tubes (BD 363083)

Hank's Balanced Salt Solution (HBSS) w/o Ca++, Mg++, Cat# 14175, Gibco BRL.
Alternatively: ThermoFisher Cat# 14170120

***Annual Visit** Red Blood Cell (Erythrocyte) Recovery

a. Spin foil-covered 1 x 2.7 ml sodium citrate tube @ 1500 RCF for 15 minutes to separate plasma and red blood cells.

b. Aliquot plasma into amber cryovials (Vitamin D-blue sticker, Ascorbic acid-red sticker) per MOO Section 14.1.1 Page 16. Remaining plasma can be aliquotted into plasma storage vials with green insert.

c. Using a transfer pipette, remove and discard the thin buffy coat layer at the plasma/red blood cell interface.

d. Transfer the red blood cells (approximately 1.2-1.5 ml) to a 12 ml round bottom polycarbonate tube and follow MOO Section 14.1.2 Page 12 beginning at item d.

SOP B: Buffy Coat Isolation

a. Draw blood in clinic (9* x 2.7 ml sodium citrate Vacutainer tubes, light blue top, NO serum separator). These are drawn instead of the usual 3 x 8 ml into CPT tubes so that the same blood volume is drawn from the subject. Invert each filled tube 6-8 times to mix the blood with the additive. *The number of tubes drawn may vary at the sites to conserve them, during this supply shortage.

b. Combine the contents of all the sodium citrate tubes into a 15ml or 50 ml conical centrifuge tube, depending on the total volume drawn.

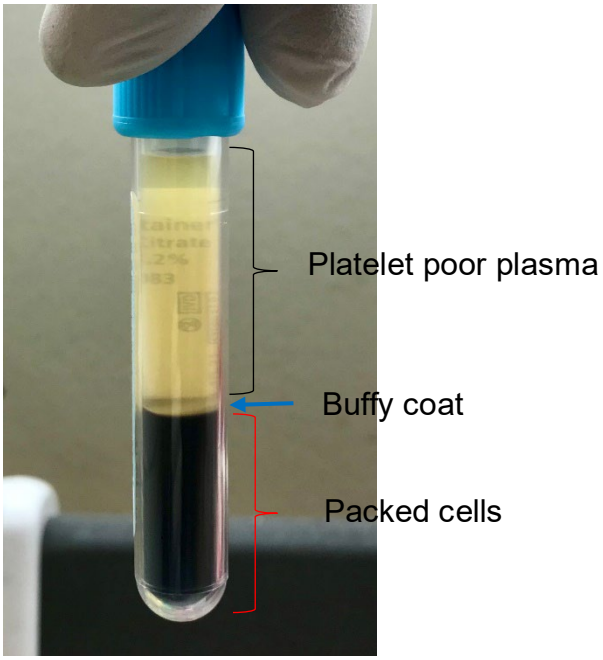
c. Centrifuge the pooled, citrated blood for 15 minutes at 1800g , ambient, to achieve platelet poor plasma

d. Carefully draw off and reserve the plasma layer without disturbing the cells underneath it. Aliquot the harvested plasma into cryovials according to the MOO section 14.1.2 and the SCF. Leave a thin layer of plasma just above the buffy coat, to avoid drawing up the buffy coat cells with your plasma.

e. Harvest the thin buffy coat layer lying on top of the packed red cells, using a disposable transfer pipette or micropipettor (for optimal control). Some plasma and some red cells will inevitably be collected along with the buffy coat cells, making it "dirty" or mixed with plasma and red cells.

f. Transfer the "dirty" buffy coat to a 2ml cryovial with no cap insert.

g. Store cryovial at -70°C to -80°C immediately after processing.



Plasma Aliquot Schedule:

3 month clinic visit

a. 0.3 ml of plasma into a 0.5 ml cryovial with a white insert for enterovirus and rotavirus PCR.
b. 0.1 ml of plasma into a 0.5 ml cryovial with a pink insert for enterovirus and rotavirus antibodies.
c. 0.4 ml of plasma into a 0.5 ml cryovial with an orange insert for additional infectious agents.
d. 0.05 ml of plasma into a 0.5 ml **amber** cryovial with a baby blue cap sticker on top for vitamin D.
e. Any additional plasma into a 2.0 ml cryovial with a green insert for storage at the repository.

6 month clinic visit

a. 0.3 ml of plasma into a 0.5 ml cryovial with a white insert for enterovirus and rotavirus PCR.
b. 0.1 ml of plasma into a 0.5 ml cryovial with a pink insert for enterovirus and rotavirus antibodies.
c. 0.4 ml of plasma into a 0.5 ml cryovial with an orange insert for additional infectious agents.
d. 0.18 ml of plasma into a 0.5 ml **amber** cryovial with a baby blue cap sticker on top for vitamin D, alpha-tocopherol, gamma tocopherol, and carotenoids.
e. 0.05 ml of plasma into a 0.5 ml **amber** cryovial with a red cap sticker on top for ascorbic acid. The 0.5 ml amber cryovial

should contain 0.2 ml of 5% (50 g/l) trichloracetic acid (TCA) + 200 mg disodium EDTA /l. Cap and mix thoroughly.

f. Any additional plasma into a 2.0 ml cryovial with a green insert for storage at the repository.

9 month clinic visit

a. 0.3 ml of plasma into a 0.5 ml cryovial with a white insert for enterovirus and rotavirus PCR.
b. 0.1 ml of plasma into a 0.5 ml cryovial with a pink insert for enterovirus and rotavirus antibodies.
c. 0.4 ml of plasma into a 0.5 ml cryovial with an orange insert for additional infectious agents.
d. 0.05 ml of plasma into a 0.5 ml **amber** cryovial with a baby blue cap sticker on top for vitamin D.
e. Any additional plasma into a 2.0 ml cryovial with a green insert for storage at the repository.

12 month clinic visit

a. 0.3 ml of plasma into a 0.5 ml cryovial with a white insert for enterovirus and rotavirus PCR.
b. 0.1 ml of plasma into a 0.5 ml cryovial with a pink insert for enterovirus and rotavirus antibodies.
c. 0.4 ml of plasma into a 0.5 ml cryovial with an orange insert for additional infectious agents.
d. 0.18 ml of plasma into a 0.5 ml **amber** cryovial with a baby blue cap sticker on top for vitamin D, alpha-tocopherol, gamma tocopherol, and carotenoids.
e. 0.05 ml of plasma into a 0.5 ml **amber** cryovial with a red cap sticker on top for ascorbic acid. The 0.5 ml amber cryovial should contain 0.2 ml of 5% (50 g/l) trichloracetic acid (TCA) + 200 mg disodium EDTA /l. Cap and mix thoroughly.
f. Any additional plasma into a 2.0 ml cryovial with a green insert for storage at the repository.

15, 18, 21 month clinic visits

a. 0.3 ml of plasma into a 0.5 ml cryovial with a white insert for enterovirus and rotavirus PCR.
b. 0.1 ml of plasma into a 0.5 ml cryovial with a pink insert for enterovirus and rotavirus antibodies.
c. 0.4 ml of plasma into a 0.5 ml cryovial with an orange insert for additional infectious agents.
d. Any additional plasma into a 2.0 ml cryovial with a green insert for storage at the repository.

24 month clinic visit

a. 0.3 ml of plasma into a 0.5 ml cryovial with a white insert for enterovirus and rotavirus PCR.
b. 0.1 ml of plasma into a 0.5 ml cryovial with a pink insert for enterovirus and rotavirus antibodies.
c. 0.4 ml of plasma into a 0.5 ml cryovial with an orange insert for additional infectious agents.
d. 0.18 ml of plasma into a 0.5 ml **amber** cryovial with a baby blue cap sticker on top for vitamin D, alpha-tocopherol, gamma tocopherol, and carotenoids.
e. 0.05 ml of plasma into a 0.5 ml **amber** cryovial with a red cap sticker on top for ascorbic acid. The 0.5 ml amber cryovial should contain 0.2 ml of 5% (50 g/l) trichloracetic acid (TCA) + 200 mg disodium EDTA /l. Cap and mix thoroughly.
f. Any additional plasma into a 2.0 ml cryovial with a green insert for storage at the repository.

27 - 33 month clinic visits

a. 0.3 ml of plasma into a 0.5 ml cryovial with a white insert for enterovirus and rotavirus PCR.
b. 0.1 ml of plasma into a 0.5 ml cryovial with a pink insert for enterovirus and rotavirus antibodies.
c. 0.4 ml of plasma into a 0.5 ml cryovial with an orange insert for additional infectious agents.
d. Any additional plasma into a 2.0 ml cryovial with a green insert for storage at the repository.

36 month – 15 year clinic visits

a. 0.3 ml of plasma into a 0.5 ml cryovial with a white insert for enterovirus and rotavirus PCR.
b. 0.1 ml of plasma into a 0.5 ml cryovial with a pink insert for enterovirus and rotavirus antibodies.
c. 0.4 ml of plasma into a 0.5 ml cryovial with an orange insert for additional infectious agents.
d. Aliquot at least 0.4 mL of plasma into a 0.5 mL cryovial with a violet cap insert for additional plasma aliquot tube 1
e. Aliquot at least 0.4 mL of plasma into a 0.5 mL cryovial with a violet cap insert for additional plasma aliquot tube 2
f. Any additional plasma should be aliquoted according to the following specifications into a 2.0 ml cryovial with a green insert for storage at the repository:
   Aliquoting schedule for autoantibody positive subjects (subjects who are on the 3 month visit schedule after 48 months of age):
   i. 0.5 ml should be aliquoted into each of the first three storage tubes

ii. Then 1.0 ml should be aliquoted into the =next three storage tubes
iii. Then 1.5 ml should be aliquoted into the next eight storage tubes
iv. If there is not enough plasma to make a 0.5 ml aliquot or 1.0 ml aliquot, the minimum volume to aliquot into a tube is 0.1 ml. If there is not at least 0.1 ml left, then the remaining plasma should be added to the last aliquoted tube and the sample volume should be accurately recorded on the SCF.
    1. For example: If a total of 3.6 ml of plasma is collected for storage, the first 1.5 ml will be aliquoted into three 0.5 ml aliquots, then - 1.5 ml into the next storage tube and then 0.6 ml into the fifth storage tube.
        a. NOTE: If the remainder was less than 0.1 ml, the remainder would be added to the 1.5 ml in the fourth tube.
v. This aliquoting scheme will yield a maximum of 14 plasma storage tubes holding a maximum total volume of 16.5 ml. If any excess, add to the last 1.5 ml storage tube.

Aliquoting schedule for autoantibody negative subjects (subjects who are on the 6 month visit schedule after 48 months of age):

i. 0.5 ml should be aliquoted in the first storage tube
ii. Then 1.6 ml should be aliquoted into the next storage tube
iii. Then 1.8 ml should be aliquoted in the next eight storage tubes
iv. If there is not enough plasma to make a 0.5 ml aliquot or 1.5 ml aliquot, the minimum volume to aliquot into a tube is 0.1 ml. If there is not at least 0.1 ml left, then the remaining plasma should be added to the last aliquoted tube and the sample volume should be accurately recorded on the SCF.
    1. For example: If a total of 3.6 ml of plasma is collected for storage, the first 0.5 ml will be aliquoted into the first storage tube, then 3.0 ml into the next two storage tubes and finally 0.1 ml in the fourth storage tube.
        a. NOTE: If the remainder was less than 0.1 ml, the remainder would be added to the 1.0 ml in the fifth tube.

v. This aliquoting scheme will yield a maximum of 10 plasma storage tubes holding a maximum total volume of 16.5 ml. If any excess, add to the 1.6 ml storage tube.

>24 month yearly additional aliquot

a. 0.18 ml of plasma into a 0.5 ml **amber*** cryovial with a baby blue cap sticker on top for vitamin D, alpha-tocopherol, gamma tocopherol, and carotenoids.
b. 0.05 ml of plasma into a 0.5 ml **amber*** cryovial with a red cap sticker on top for ascorbic acid. The 0.5 ml amber cryovial should contain 0.2 ml of 5% (50 g/l) trichloracetic acid (TCA) + 200 mg disodium EDTA /l. Cap and mix thoroughly.

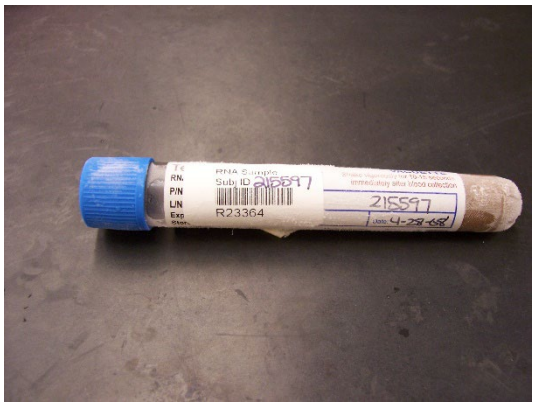
*Beginning in December 2020 the sterile 0.5 ml amber cryovials that TEDDY had used throughout the study became difficult to purchase due to supply issues. For periods of time non-sterile 0.5 ml amber cryovials were used. Appendix 1 provides instructions for the Clinical Centers for the autoclave sterilization of these tubes.

Plasma, PBMC, Buffy Coat and Erythrocytes Storage

Enter each Plasma, PBMC, buffy coat and Erythrocytes sample's information onto the Sample Collection Forms (see Section 14.1.7.) then store Plasma, Buffy Coat and Erythrocytes and PBMC samples at -70°C to -80°C, immediately after processing, until shipping.

14.1.3. RNA – ABI Tube – For further details see the PowerPoint presentation and video clips in the folder entitled "RNA sample collection presentation and training videos_September 2009" which can be found in the MOO section of the TEDDY website (NOTE: the presentation indicates that samples should be left out at room temperature for at least 2 hours - if the last collected samples of the day cannot be left out for 2 hours the RNA lab prefers that you leave the tube out at room temperature overnight rather than freezing the tube before the 2 hours has elapsed. Under special circumstances when the tubes cannot be frozen between 2 hours and one day, the tubes may be left at room temperature for up to three days.)

a. Place vial barcode sticker, received from the DCC, on ABI tube. Sticker should be placed on ABI tube length-wise, for easy scanning:



b. After transferring the blood into the ABI tube, shake the tube VIGOROUSLY with a full range of motion for a minimum of 15 seconds to mix the blood with the stabilizing agent contained in tube and to lyse the red cells. Tubes should be shaken vigorously enough that contents will foam.
c. Enter each RNA sample's information onto the Sample Collection Forms (see Section 14.1.7.)
d. Let sample sit at room temperature for 1-2 hours before transferring to -70°C.
e. **Do not** store tube in styrofoam racks; use open racks or boxes.
f. Freeze at-70°C until ready to send to Repository.
g. The blood will then be shipped directly to the Repository.

14.1.4. Whole Blood - EDTA Tube

Whole Blood aliquoting

9 month clinic visit -A whole blood sample will be drawn from subjects at the 6, 9 12 or 15 month clinic visit for better definition and additional genotyping. Sites are encouraged to complete this collection by the earliest visit with a full volume blood draw, but in all cases by the 15 month visit. If the HLA confirmation sample is collected at the 6 month visit, only 0.5 mL of blood is required to be collected for this sample. If the HLA confirmation sample is collected at the 9, 12 or 15 month visit 1 mL of blood should be collected for this sample.

a. Transfer 1 ml of whole blood into a plastic EDTA tube (glass tubes should not be used). Mix the contents of the tube gently by turning it up and down five times immediately after sampling. Aliquot the 1 ml of blood from EDTA tube into a 4 ml round bottom etched TEDDY cryovial and cap for additional HLA genotyping.

4 Year clinic visit – A whole blood sample will be drawn from subjects at the 4 year clinic visit. If the sample cannot be collected at the 4 year visit, it

should be attempted to be collected at the next scheduled visit, but must be collected by the 5 year 9 month visit.

a. Transfer 5 ml of whole blood into a plastic EDTA tube (glass tubes should not be used). Mix the contents of the tube gently by turning it up and down five times immediately after sampling. Aliquot the 5 ml of blood from EDTA tube into an 8 ml etched TEDDY cryovial and cap for non-HLA genotyping.

6 Year clinic visit - A whole blood sample will be drawn from subjects at the 6 year clinic visit. If the sample cannot be collected at the 6 year visit, collection should be attempted at the next scheduled visit.

a. Transfer 2 ml of whole blood into a plastic EDTA tube (glass tubes should not be used). Mix the contents of the tube gently by turning it up and down five times immediately after sampling. Aliquot the 2 ml of blood from EDTA tube into a 4 ml etched TEDDY cryovial and cap for Whole Blood Sample storage.

Whole Blood Storage
Enter each Whole Blood sample's information onto the Sample Collection Forms (see Section 14.1.7.) then store Whole Blood samples at -70°C until shipping. 9 month HLA confirmation sample will be shipped to the HLA Reference Lab for additional HLA genotyping. 4 year non-HLA genotyping sample will be shipped directly to the NIDDK Repository for storage. Clinical Centers will ship the 6 year Whole Blood Storage Sample directly to the NIDDK Repository for storage.

14.1.5. HbA1c – EDTA Tube

The HbA1c sample will be drawn at the next TEDDY visit and every visit thereafter from children who are positive at the 9 month visit or later for at least one autoantibody (regardless of autoantibody positivity confirmation or persistence). Following this logic, the first possible visit that the HbA1c sample could be collected at is the 12 month visit.

a. Place vial barcode sticker, received from the DCC, on a 0.5 mL EDTA bullet tube. Sticker should be placed on EDTA tube length-wise, for easy scanning.
b. Draw 0.1 - 0.25 mL of whole blood into the 0.5 mL EDTA bullet tube (the lab has indicated that as long as the tube contains at least 0.1 ml of blood they will be able to complete HbA1c testing).
c. Immediately mix the blood with the EDTA by inverting the tube gently 6-8 times, avoiding jarring or shaking. DO NOT CETRIFUGE.
d. Enter each HbA1c sample's information onto the Sample Collection Forms (see MOO Section 14.1.7.)

e. Freeze sample at-70°C immediately after mixing until ready to send to HbA1c central laboratory.
f. The blood sample will next be shipped on dry ice in the EDTA tube directly to the HbA1c Laboratory for HbA1c measurement. Sites should send samples to the lab on a quarterly basis.

All HbA1c results are reported to the clinic following the TEDDY subject. If the HbA1c value is ≥42 (6.0 %), a pediatric endocrinologist is informed. The family is educated to be aware of diabetes symptoms and follow-up is recommended as follows:

a. OGTT will be scheduled, preferentially within 30 days and/or
b. The family may be given a glucose meter and informed to test fasting and post-prandial glucose for 3-7 days and report the values back to the study staff. Families are instructed to call immediately if they measure two values ≥200 mg/dL (≥11.1 mmol/L) or one value ≥300 mg/dL (16.6 mmol/L). Written information about when to perform glucose checks and how to respond to values is preferred.

14.1.6. Parental and sibling DNA collection for heritability analyses – EDTA Tube

One 5 mL blood sample will be obtained from each parent and sibling (both full and half siblings) of the TEDDY child for heritability analyses. These samples can be collected at any time during the study. The sample will be drawn into an EDTA tube then transferred to an externally threaded cryovial. The sample will then be sent to the NIDDK repository for storage.

An optional 2 ml blood sample will be obtained at the parent's request from each parent and sibling of the TEDDY child for a one time screening for islet autoantibodies. The sample will be drawn into an SST tube and will be tested at the Denver Reference Lab for the US sites and the Bristol Reference Lab for European sites. Confirmation at the other Reference Laboratory will not be performed for any samples, including samples testing positive for islet autoantibodies. Local sites will determine the format for relaying islet antibody results to family members from their site.

> NOTE: The father, mother and sibling autoantibody results will be automatically emailed to the corresponding Clinical Center when the Autoantibody lab uploads the results. The "Test Name" listed for the sample in the results file will be either "Biological Mother's Autoantibody Sample", "Biological Father's Autoantibody Sample" or "Biological Sibling's Autoantibody Sample", the family ID and relative ID associated with the sample will be indicated in separate fields in the results file.

Instructions for parent and sibling DNA sample processing:

a. Transfer 5 ml of whole blood into a plastic 6 ml EDTA tube (glass tubes should not be used).
b. Mix the contents of the tube gently by turning it up and down five times immediately after sampling.
c. Aliquot the 5 ml of blood from EDTA tube into an 8 ml etched TEDDY cryovial and cap.

Instructions for parent and sibling antibody sample processing:

a. Allow to clot for at least 30 minutes in a vertical position. If fibrin clumps occur in the centrifuged serum, increase the clotting time to 45 minutes before centrifugation.
b. Centrifuge at room temperature at full speed (between 1100 and 1300g) for 10 minutes for a swinging head unit or 15 minutes for a fixed angle unit (balance tube in centrifuge). The serum will be separated from clot by the gel barrier.
c. Transfer 0.1 ml of serum into a 0.5 ml cryovial with a red insert.

SCF and shipping instructions for parent and sibling DNA samples and antibody samples:

a. Go to the corresponding Sample Collection Form:
    i. These SCFs can be found under the Additional Study Forms drop-down menu at the upper right-hand corner of the Participant's Details Page – you will find a separate form for each relative: "Biological Father's DNA Sample Collection Form", "Biological Mother's DNA Sample Collection Form" and "Sibling's DNA Sample Collection Form" (if the TEDDY subject has multiple siblings that samples have been collected from, choose a new sibling SCF for each sibling).
    ii. Choose the desired form and click the "Select Form" button that is below the dropdown menu.
    iii. If the family only has one child enrolled in the TEDDY study:
        1. Enter the sample information on the corresponding family member's SCF and answer the questions at the bottom of the form. Leave the family ID field blank – it will be automatically assigned by the DCC at the time of the first save of any of the family member SCFs. Also leave the Relative ID field blank, an ID specific to that family member will be assigned by the DCC at the time of the save of the SCF.
            a. NOTE: on the Mother's DNA SCF the question "Does or did the biological mother have diabetes?" applies to if the mother has ever had gestational diabetes, not just gestational diabetes with the TEDDY subject.

i. If the mother had gestational diabetes with several pregnancies, the age or year of diagnosis should relate to the first time she developed gestational diabetes

2. Click the save button and close the form.
3. Repeat this as necessary for each family member that samples have been collected from.

iv. If the family has more than one child enrolled in the TEDDY study, samples only need to be collected from each family member one time.

1. If the family has more than one child enrolled in the TEDDY study and a family ID has already been assigned to one of the TEDDY children (family ID is automatically assigned by the DCC at the time of the first save of any of the family member SCFs), enter that family ID in the corresponding field on one of the family member's SCFs, that samples have been collected from, for the other TEDDY subject(s) that has not yet been associated with this family ID. This family ID will automatically prepopulate on all of the other family member SCFs for this subject. At analysis time, this will allow the DCC to know that the children are related and that the family member's sample information can also be associated with this TEDDY subject.
2. If the family has more than one child enrolled in the TEDDY study and a relative ID has already been assigned to that family member (relative ID is automatically assigned by the DCC), enter that relative ID in the corresponding field on the other TEDDY subject's relative's SCF. For example if Subject A and Subject B are full siblings, both enrolled in the TEDDY Study and their biological mother has been assigned Relative ID 12345 on the Mother's DNA SCF associated with Subject A, site would enter Relative ID 12345 on the Mother's DNA SCF associated with Subject B.
3. If the specific family member's sample information and answers to questions at the bottom of the form have already been entered on the other subject's family member SCF then this information does not need to be re-entered on this TEDDY subject's family member SCF. All that must be entered is the family ID on the first save of the first family member's SCF and the corresponding relative ID on each family member's SCF.

NOTE: If there is more than one child from one family enrolled in TEDDY, the non-HLA genotyping sample can be used as the sibling DNA

sample (a new blood sample does not need to be collected for the sibling DNA sample):

i. In the vial barcode number section of the Sibling DNA SCF mark the check box next to "This child is also enrolled in the TEDDY study, use 48 month non-HLA genotyping sample for this sample".
ii. Enter the vial barcode number of the 48 month non-HLA genotyping sample in the provided data field (no other information related to the 48 month non-HLA genotyping sample should be entered).
iii. Repeat steps i and ii for all TEDDY subjects within a family that this applies to

NOTE: Once you save a SCF with only the family ID and Relative ID entered, you will not be able to make any changes to the SCF. If you need a correction made, please contact the DCC.

4. If the specific family member's sample information and answers to questions at the bottom of the form have NOT been entered on the other subject's family member SCF, then enter the information on this subject's family member SCF and if the family member ID has not yet been prepopulated on the form also enter it and enter the corresponding relative ID of the family member.
5. Click the save button and close the form.
6. Repeat this as necessary for each family member that samples have been collected from.

b. Store the samples at -70°C until shipping.
c. The DNA samples will then be sent to the Repository for long-term storage . The samples will be shipped on dry ice overnight.
d. The US sites will then ship the antibody samples to the US Autoantibody Lab and the European sites will ship the antibody samples to the European Autoantibody Lab. The samples will be shipped on dry ice overnight.

<u>Tracking System instructions for parent and sibling DNA samples and antibody samples</u>

If the site is unable to collect both a DNA sample and antibody sample from a parent or sibling, the site should mark a not done reason in the tracking system of the SCF:

a. Go to the corresponding Sample Collection Form:

1. These SCFs can be found under the Additional Study Forms drop-down menu at the upper right-hand corner of the Participant's Details Page – you will find a separate form for each relative: "Biological Father's DNA Sample Collection Form", "Biological Mother's DNA Sample Collection Form" and "Sibling's DNA Sample Collection Form" (if the TEDDY subject has multiple siblings, choose a new sibling SCF for each sibling).
2. Choose the desired form and click the "Select Form" button that is below the dropdown menu.

b. Select "Tracking System" button at top of SCF.
c. A new window will open which allows the site to enter the reason why the samples were not collected.
d. Once the not done reason has been selected, click "Save Form".

NOTE: If site marks a not done reason in the tracking system and then is later able to collect the sample, site should contact the DCC to clear the not done reason from the tracking system.

Once the Participant's Details Page has been refreshed, you will see "Biological Father's DNA Sample Collection Form", "Biological Mother's DNA Sample Collection Form" or "Sibling's DNA Sample Collection Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

a. Click on the form link under 'Completed Additional Study Forms'
b. A new window will open which will have a link to the tracking system form that has been saved for this subject.
c. Click on the 'Tracking' link to open up the specific tracking system form for this subject.

14.1.7. Blood Sample Collection Forms (SCFs)

The SCFs contain constraints that prevent a vial barcode number from being saved more than once. If you try to save a vial barcode number that has already been saved, an error message will appear that explains why the new information cannot be saved. If the vial barcode number that you are trying to save is correct and the same vial barcode number has been entered (and saved) incorrectly for a subject that is within your clinical center, please try to determine the mistake that was made and correct appropriately on the TEDDY website (the Local Code, Subject ID, Visit Name and Test Name associated with the other sample will be provided in the error message) – if you are unable to make the correction yourself contact the DCC at **TEDDY@epi.usf.edu** to make the correction for you. If the sample has already been sent to the Repository or Lab, please contact the Repository or Lab and the DCC with the correct information; once the Repository or Lab

verifies that the new information you have given is correct then you should correct this information on the TEDDY website – if you are unable to make the correction yourself contact the DCC at **TEDDY@epi.usf.edu** to make the correction for you. If the vial barcode number was incorrectly entered and saved for a subject that is not within your clinical center, please contact the DCC at **TEDDY@epi.usf.edu**

There are two ways to retrieve the subject's Blood Sample Collection Form, please see instructions below.

"Sample Collection Form" link:

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Sample Collection Forms" link under "Data Management" on the left navigational toolbar.
3. Enter both the Subject ID and Local Code of the subject.
4. Select the desired visit.
5. Select the desired Sample Collection Form (i.e. serum, plasma, RNA).
6. Subject ID, Local Code, and Clinical Center fields will be prepopulated on the Sample Collection Form.
7. Choose the correct Visit Location Code from the drop down menu - this is the location where the TEDDY visit took place. Drop-down list based upon TEDDY Clinical Center field.
8. Enter the Date of Draw of the blood sample (DD/MMM/YYYY).

If the blood sample was processed according to standard TEDDY protocol (i.e. the Long-Distance protocol was not followed) follow the instructions directly below; if PBMC samples were isolated according to the standard TEDDY protocol (i.e. the Long-Distance protocol was not followed) and were either processed the same day or were processed the next day follow the instructions directly below:

   a. Mark the "Sample processed according to standard protocol or Standard protocol followed, insufficient volume" checkbox (note: you should also mark this box when there is an insufficient volume of blood for the Plasma and/or RNA sample, but the Serum sample was processed following standard protocol). If the sample is a serum or plasma sample proceed to step 8.b directly below; if no plasma aliquots were able to be collected proceed to step 9 instead. For any other type of sample proceed to step 9.
   b. For collected serum and plasma samples ONLY:
      i. Enter the time the sample was drawn.

ii. Enter the date the sample was processed.
iii. Enter the time the sample was processed (this is the time the sample was put in the freezer). If the sample is a serum sample proceed to step 9; if the sample is a plasma sample and no PBMC samples were isolated proceed to step 9; if the sample is a plasma sample and PBMC samples were isolated proceed to step 8.b.iv directly below.
iv. For collected plasma samples that will be used for PBMC isolation ONLY: enter the estimated total blood volume (within approximately 1 mL) of whole blood added to all CPT tubes from this draw used for PBMC isolation, prior to processing. This is the amount of whole blood added from syringe, not the final volume including reagent in the tube. If you drew directly into the CPT tube, use a calibrated tube to measure volume of whole blood added.
v. For collected plasma samples: select the collection tube size that was used. If sample was collected during COVID-19 CPT tube shortage and CPT tubes were not available, mark the check box "CPT tubes are unavailable, alternate 2.7 ml sodium citrate tube was used instead". Proceed to step 9.

If the sample was processed according to the Long-Distance protocol:

a. The Long-Distance protocol lab should complete all parts of section 3c on the Physical Exam Form (Date sample was drawn, Time sample was drawn, Date sample was shipped and if applicable estimated total blood volume (within approximately 1 mL) of whole blood added to all CPT tubes from this draw used for PBMC isolation, prior to processing) and either the lab or subject then returns the form with the samples to the TEDDY Clinical Center.

NOTE: The only data collected in section 3c of the Physical Exam Form that needs to be re-entered on the sample's corresponding SCF is the date the sample was drawn. However when the TEDDY site receives the Long-Distance protocol sample(s) and Physical Exam Form back, the TEDDY staff member should verify that the CPT volume has been entered on the Physical Exam Form by the Long-Distance Protocol lab. If the CPT volume has not been entered then the TEDDY staff member should estimate the volume and enter it in section 3c of the Physical Exam Form.

NOTE: If sample was drawn/collected in a Long-Distance protocol lab that is in a different time zone than the

TEDDY Clinical Center the time the sample was drawn and the time the sample was processed should be indicated in the time zone of the Clinical Center and this should be noted on the Physical Exam Form source document received from the Long-Distance protocol lab.

b. If there was an insufficient blood volume for all Plasma and/or all RNA samples on the particular SCFs, but there was enough for at least one of the Serum samples (note: if there was not enough blood for at least one Serum sample then you should indicate the 'not done' reason for each type of sample in the tracking system and not use the SCFs) mark the "Long-Distance Protocol Insufficient Volume (for all tests on this SCF)" checkbox on the Plasma and/or RNA SCF and continue to step 9 **OR**
c. If there was a sufficient amount of blood for at least one of the samples on the SCF indicate the date and time that the sample was processed (this is the time the sample was put in the freezer), select the collection tube size that was used (If sample was collected during COVID-19 CPT tube shortage and CPT tubes were not available, mark the check box "CPT tubes are unavailable, alternate 2.7 ml sodium citrate tube was used instead") and continue to step 9 (Long-Distance protocol lab that actually collected the sample should have indicated the date the sample was drawn, time the sample was drawn, date the sample was shipped and if applicable estimated total blood volume (within approximately 1 mL) of whole blood added to all CPT tubes from this draw used for PBMC isolation, prior to processing) in Section 3c of the corresponding Physical Exam Form).

9. Find the row containing the "Test Name" (e.g. Autoantibody Reference Lab Sample, Autoantibody Repository Sample, RNA Sample, Vitamin D Sample, etc.) of the sample in the vial you would like to scan. If an insufficient blood volume amount was obtained, and there is not enough blood for that particular Test Name, check the "Insufficient Blood Volume" Box* in that row, repeat this step as necessary then continue to step 16; if there is a sufficient amount of blood go to step 10.
10. Place cursor in the "Vial Barcode Number" box in this row.
11. Scan the preprinted barcode located on the cryovial containing this particular sample. If you have collected PBMC samples, indicate the lot number(s) of the freezing media serum in the fields provided in the PBMC Tube #1 test name field. Sites should enter the lot number for both solution A and solution B. If solution A and B come from the same lot number, the lot number should be entered in both fields.
12. In the provided space, enter the sample volume (mL) contained in the cryovial. For PBMC samples enter the total volume of cells in the

cryovial (after addition of all freezing media), final concentration of cells in the cryovial (after addition of all freezing media), isolating lab's observed viability of cells and select the method used for counting cells and determining viability for each PBMC sample.

NOTE: For PBMC cell count "X 10^6" has been added to the SCF after the cell count field, therefore, in the cell count field, the site only needs to enter the number that will be multiplied by 10^6

13. In the provided space enter box number (or pouch number for RNA samples) and space number where the sample will be stored.
14. Place the cryovial in the exact freezer box or pouch (2" freezer box with 81 cell divider insert for samples sent to the Repository, and Autoantibody Reference Labs; 3" freezer box with a 36 cell divider insert for samples sent to the HLA Reference Lab; Saf-T-Pak pouch for samples sent to the RNA Lab) and space number that you entered on the SCF for that particular sample.
15. Repeat steps 9-14 as necessary.
16. When all samples for this specific SCF have been entered, click the "Save Form" button.
17. Continue this process for other subjects; when all samples have been entered into the SCFs and placed into the freezer boxes, store the boxes in the freezer at -70 °C.

*Insufficient Blood Volume should only be indicated when some blood was able to be collected during the blood draw, but there was just not enough blood for that particular aliquot. When **no** blood is able to be obtained during the blood draw a Not Done reason should be indicated in the tracking system instead of indicating Insufficient Blood Volume on the SCF (see MOO section 17.2.8. for instructions).

"Enter/Edit/View" Link:

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject by entering one of the following: 1) Local Code and Subject ID 2) Local Code and Date of Birth 3) Date of Birth Range 4) Clinical Center and Subject ID 5) Clinical Center and Local Code or 6) Clinical Center and/or Visit Location Code.
4. Under "Search Results", click on the Local Code of the desired subject.
5. Choose the desired Sample Collection Form by clicking on the links under "Event Title" (i.e. Serum Sample, Plasma Sample, RNA Sample)
6. Subject ID, Local Code, and Clinical Center fields will be prepopulated on the Sample Collection Form.
7. Choose the correct Visit Location Code from the drop down menu this is the location where the TEDDY visit took place. Drop-down list based upon TEDDY Clinical Center field.
8. Enter the Date of Draw of the blood sample (DD/MMM/YYYY).

If the blood sample was processed according to standard TEDDY protocol (i.e. the Long-Distance protocol was not followed) follow the instructions directly below; if PBMC samples were isolated according to the standard TEDDY protocol (i.e. the Long-Distance protocol was not followed) and were either processed the same day or were processed the next day follow the instructions directly below:

a. Mark the "Sample processed according to standard protocol or Standard protocol followed, insufficient volume" checkbox (note: you should also mark this box when there is an insufficient volume of blood for the Plasma and RNA sample, but the Serum sample was processed following standard protocol). If the sample is a serum or plasma sample proceed to step 8.b directly below; if no plasma aliquots were able to be collected proceed to step 9 instead. For any other type of sample proceed to step 9.

b. For collected serum and plasma samples ONLY:
   i. Enter the time the sample was drawn.
   ii. Enter the date the sample was processed.
   iii. Enter the time the sample was processed (this is the time the sample was put in the freezer). If the sample is a serum sample proceed to step 9; if the sample is a plasma sample and no PBMC samples were isolated proceed to step 9; if the sample is a plasma sample and PBMC samples were isolated proceed to step 8.b.iv directly below.
   iv. For collected plasma samples that will be used for PBMC isolation ONLY: enter the estimated total blood volume (within approximately 1 mL) of whole blood added to all CPT tubes from this draw used for PBMC isolation, prior to processing. This is the amount of whole blood added from syringe, not the final volume including reagent in the tube. If you drew directly into the CPT tube, use a calibrated tube to measure volume of whole blood added.
   v. For collected plasma samples: select the collection tube size that was used (If sample was collected during COVID-19 CPT tube shortage and CPT tubes were not available, mark the check box "CPT tubes are unavailable, alternate 2.7 ml sodium citrate tube was used instead"). Proceed to step 9.

If the sample was processed according to the Long-Distance protocol:

a. The Long-Distance protocol lab should complete all parts of section 3c on the Physical Exam Form (Date sample was drawn, Time sample was drawn, Date sample was shipped and if applicable estimated total blood volume (within approximately 1 mL) of whole blood added to all CPT tubes from this draw used for PBMC isolation, prior to processing) and either the lab or subject then returns the form with the samples to the TEDDY Clinical Center.

   NOTE: The only data collected in section 3c of the Physical Exam Form that needs to be re-entered on the sample's corresponding SCF is the date the sample was drawn. However when the TEDDY site receives the Long-Distance protocol sample(s) and Physical Exam Form back, the TEDDY staff member should verify that the CPT volume has been entered on the Physical Exam Form by the Long-Distance Protocol lab. If the CPT volume has not been entered then the TEDDY staff member should estimate the volume and enter it in section 3c of the Physical Exam Form.

   NOTE: If sample was drawn/collected in a Long-Distance protocol lab that is in a different time zone than the TEDDY Clinical Center the time the sample was drawn and the time the sample was processed should be indicated in the time zone of the Clinical Center and this should be noted on the Physical Exam Form source document received from the Long-Distance protocol lab.

b. If there was an insufficient blood volume for all Plasma and/or all RNA samples on the particular SCFs (but there was enough for at least one of the Serum samples – note: if there was not enough blood for at least one Serum sample then you should indicate the 'not done' reason for each type of sample in the tracking system and not use the SCFs) mark the "Long-Distance Protocol Insufficient Volume (for all tests on this SCF)" checkbox on the Plasma and/or RNA SCF and continue to step 9 **OR**

c. If there was a sufficient amount of blood for at least one of the samples on the SCF indicate the date and time that the sample was processed (this is the time the sample was put in the freezer), select the collection tube size that was used and continue used (If sample was collected during COVID-19 CPT tube shortage and CPT tubes were not available, mark the check box "CPT tubes are unavailable, alternate 2.7 ml sodium citrate tube was used instead") to step 9 (Long-Distance Protocol lab that actually collected the sample should have indicated the date the sample was drawn, time the sample was drawn, date the sample was shipped and if applicable estimated

total blood volume (within approximately 1 mL) of whole blood added to all CPT tubes from this draw used for PBMC isolation, prior to processing) in Section 3c of the corresponding Physical Exam Form).

9. Find the row containing the "Test Name" (e.g. Autoantibody Reference Lab Sample, Autoantibody Repository Sample, RNA Sample, Vitamin D Sample, etc.) of the sample in the vial you would like to scan. If an insufficient blood volume amount was obtained, and there is not enough blood for that particular Test Name, check the "Insufficient Blood Volume" Box* in that row, repeat this step as necessary then continue to step 16; if there is a sufficient amount of blood go to step 10.
10. Place cursor in the "Vial Barcode Number" box in this row.
11. Scan the preprinted barcode located on the cryovial containing this particular sample. If you have collected PBMC samples, indicate the lot number(s) of the freezing media serum in the fields provided in the PBMC Tube #1 test name field. Sites should enter the lot number for both solution A and solution B. If solution A and B come from the same lot number, the lot number should be entered in both fields.
12. In the provided space, enter the sample volume (mL) contained in the cryovial. For PBMC samples enter the total volume of cells in the cryovial (after addition of all freezing media), the final concentration of cells in the cryovial (after addition of all freezing media), isolating lab's observed viability of cells and select the method used for counting cells and determining viability for each PBMC sample.
    NOTE: For PBMC cell count "X 10^6" has been added to the SCF after the cell count field, therefore, in the cell count field, the site only needs to enter the number that will be multiplied by 10^6
13. In the provided space enter box number (or pouch number for RNA samples) and space number where the sample will be stored.
14. Place the cryovial in the exact freezer box or pouch (2" freezer box with 81 cell divider insert for samples sent to the Repository, and Autoantibody Reference Labs; 3" freezer box with a 36 cell divider insert for samples sent to the HLA Reference Lab; Saf-T-Pak pouch for samples sent to the RNA Lab) and space number that you entered on the SCF for that particular sample.
15. Repeat steps 9-14 as necessary.
16. When all cryovials for this specific SCF have been entered, click the "Save Form" button.
17. Continue this process for other subjects; when all samples have been entered into the SCFs and placed into the freezer boxes, store the boxes in the freezer at -70 °C.

*Insufficient Blood Volume should only be indicated when some blood was able to be collected during the blood draw, but there was just not enough blood for that particular aliquot. When **no** blood is able to be obtained during the blood draw a Not Done reason

should be indicated in the tracking system instead of indicating Insufficient Blood Volume on the SCF (see MOO section 17.2.8. for instructions).

14.1.8. Shipping

ANY BETWEEN SUB-SITE TRANSPORT OF SAMPLES SHOULD BE DONE ON DRY ICE, USING AMPLE AMOUNTS TO ENSURE MAINTENANCE OF FROZEN SAMPLES AT TEMPERATURES BELOW -50°C

14.1.8.1. Blood samples shipped to Repository

Entering information into the "Sample Shipment System"

Once a month each clinical center will send bulk shipments of serum, plasma and RNA samples to the NIDDK Repository; Clinical Centers will send PBMC samples every two weeks to the Repository (PBMC samples should be shipped to the Repository in separate freezer boxes AND shipment boxes from the other samples being shipped to the Repository - upon receipt the Repository will store the samples in liquid nitrogen long-term).

1. Logon to the TEDDY website, http://teddy.epi.usf.edu/
2. Go to the "Sample Shipment System" located on the left navigational toolbar under "Data Management".
3. Enter the date of shipment.
4. If you have user access to more than one shipment origin, you will need to choose which destination the samples you are shipping are being shipped from. If you only have user access to one shipment origin, the 'Origin' drop-down menu will be defaulted to that location and you do not need to do anything.
5. Choose the "Repository" destination option under "Select where samples will be shipped to".
6. Enter the freezer box number(s) or pouch number(s) (numbers separated by commas) that you are going to be shipping that day and click "Search".
7. The Local Code, Subject ID, Clinical Center, Test Name, Vial Barcode Number, Visit Location Code, Date Draw, Box/Pouch Number, Space Number, Sample Volume, Site Number (this will only appear for samples being shipped to the Repository) and "Delete From Shipment" option will appear for all the samples that are located in the box(es).
8. Enter the tracking number and courier service for that shipment and any comments you would like to notify the lab about.
9. Click on "Print and Email Shipping List". A dialog box will open that asks "Are you sure you want to print and email the shipment list?" Press 'OK' if you do and 'Cancel' if you don't.

10. Once 'OK' has been clicked an Excel file will be created that will contain information pertaining to each sample (Vial Barcode Number, Subject ID, etc).
11. Save this file for your records; an email containing this file will automatically be sent to the DCC and to the Repository.
12. Print out a copy of this list to be shipped with the samples.
13. Repeat this process as necessary until all the boxes you will be sending that day have been entered.

"April 11, 2019 recommendation from the Repository for shipment of RNA samples:

There are three packaging scenarios we see when sites send the RNA tubes to the Repository.

- Tubes placed in bubble pouches
- Tubes placed in bubble pouches then placed in a cryobox
- Tubes placed in a cryobox in a 7x7 grid

The most secure method would be to place the tubes in a gridded cryobox. We find that the tubes will occasionally slide out of the bubble pouches and will be found scattered throughout the dry ice, which by the way would make it hard to determine which pouch which tube came from if multiple pouches are included in the shipment. Also important to share and as you mentioned below, the bubble pouches start to become brittle and tear easily due to the direct placement on the dry ice."

Packing and Shipping Instructions for US Sites:

1. Please do not ship packages on Friday. The repository is closed for business on weekends.
2. Place the 2" freezer box (PBMC samples should be shipped to the Repository in separate freezer boxes AND shipment boxes from the other samples being shipped to the Repository - upon receipt the Repository will store the samples in liquid nitrogen long-term) along with a STP-152 absorbent strip inside a STP-711 inner leak proof poly (plastic) bag. Seal the bag.
3. Place the poly bag inside a STP-714 envelope, fold over and tuck the STP-714 into pocket.
4. Place up to three filled STP-714 envelopes in the cardboard inner box, tape the box shut and place it in the middle of the cooler in the STP-320 shipper. If there are only one or two vial boxes in the shipment, fill the rest of the space inside the cardboard inner box with packing material (e.g. bubble wrap or newspaper) to prevent movement during shipment.
5. Fill the remainder of the space between the cardboard box and the inner walls of the cooler with dry ice.
6. For RNA samples:

a. Insert ABI vacutainer tubes into Safe-T-Pak pouches (each pouch holds 5 tubes). Label pouches appropriately, pouch number and spaces, as corresponds to the shipping list.
b. Place up to 3 (five tubes each set) sets of Safe-T-Pak pouches in each Ziplock bag containing absorbent material. Squeeze the air out of the bag and then close.
c. Place a layer of dry ice pellets on the bottom of the shipping box.
d. Place the Ziplock bag(s) containing the Safe-T-Pak pouches into the shipping box. Fill box with 2 stacks of pouches, leaving at least 2-3 inches of space on top for dry ice.

7. Put the lid on the cooler and place the excel printout (containing the sample information) on top of the cooler. Place the "empty packaging cover" (if included – this will be one piece of cardboard that is attached to the outside of the box) on top of the list.
8. Close and tape the outer cardboard box.
9. Place a checkmark in the block on the outer cardboard box next to "BIOLOGICAL SUBSTANCE, CATEGORY B". Do not cover this marking with labels.
10. Affix a label with your name and return address to the side of the box in the "Shipper" block.
11. Affix the repository address label to the side of the box in the "Consignee" block that reads:

Chris Deigan
Disease Prevention
Fisher BioServices
20301 Century Blvd.
Building 6, Suite 400
Germantown MD 20874

12. Affix the dry ice label below the repository address label. Enter the weight of dry ice on the label in kilograms.
13. Affix the "UN3373 BIOLOGICAL SUBSTANCE, CATEGORY B" label to the right of the dry ice label.
14. Use the pre-printed FedEx US air bill to ship the samples to the NIDDK Biosample Repository at Fisher Bioservices.
    a. In Section 1, enter the date, your name, return address and phone number. Leave "Sender's FedEx Account Number" blank
    b. Complete Section 6, Special Handling:
        i. Under "Does this shipment contain dangerous goods?" check "Yes, Shippers Declaration not required".

ii. Check the "Dry Ice" block and enter "1" and the weight of dry ice in kg.

c. Under Section 7, Payment:
   i. Enter "1" under "Total Packages".
   ii. Enter the total weight of the package under "Total Weight".

d. Follow the peel and stick instructions on the back of the air bill (no document holder required).

e. Attach the air bill to the side of the box adjacent to the labeled sie.

15. Call FedEx at 1.800.Go.FedEx® (800.463.3339) **or** go to http://www.fedex.com/us/ to schedule a pick-up
16. Notify the repository of the incoming shipment and tracking number via email (BIO-NIDDKRepository@FisherSci.com) or fax (301-515-4049) on the day the package is picked up by FedEx.

Packing and Shipping Instructions for European Sites:

1. Please plan for the arrival dates of your shipments - the repository is closed for business on weekends.
2. Place the 2" freezer box (PBMC samples should be shipped to the Repository in separate freezer boxes AND shipment boxes from the other samples being shipped to the Repository - upon receipt the Repository will store the samples in liquid nitrogen long-term) along with an absorbent strip inside the inner leak proof poly (plastic) bag. Seal the bag.
3. Place the plastic bag inside the long Tyvek envelope. Place the box inside the far end of the long pocket of the envelope. Crease the envelope near the middle, fold the envelope over, and place the end of the envelope containing the box inside the short pocket on the opposite side of the envelope. Push the box firmly into the short end of the envelope.
4. Put a layer of dry ice in the bottom of the box. Place the Tyvek envelopes containing boxes on the dry ice.
5. Fill the remainder of the space in the shipper with dry ice.
6. For RNA samples:
   a. Insert ABI vacutainer tubes into Safe-T-Pak pouches (each pouch holds 5 tubes). Label pouches appropriately, pouch number and spaces, as corresponds to the shipping list.
   b. Place up to 3 (five tubes each set) sets of Safe-T-Pak pouches in each Ziplock bag containing absorbent material. Squeeze the air out of the bag and then close.
   c. Place a layer of dry ice pellets on the bottom of the shipping box.
   d. Place the Ziplock bag(s) containing the Safe-T-Pak pouches into the shipping box. Fill box with 2 stacks of

pouches, leaving at least 2-3 inches of space on top for dry ice.

7. Put the foam insert, or lid, on top of the dry ice in the opening. Place a copy of the manifest shipping form inside a zip-lock bag, and set it on top of the foam insert under the lid flaps.
8. Close and tape the cardboard box.
9. Attach all labels to the same side of the box:
   a. Stick the dry ice label on the side of the box in the upper right corner. Enter the weight of dry ice on the label.
   b. Place the "UN3373 Diagnostic Specimens" label on the top, center, to the left of the dry ice label.
   c. Stick the small address label below the "Up" arrows that reads:

Chris Deigan
Disease Prevention
Fisher BioServices
20301 Century Blvd.
Building 6, Suite 400
Germantown MD 20874
USA

10. Use the preprinted World House Air Way Bill (HAWB) to ship the samples to the NIDDK Biosample Repository at Fisher Bioservices.
    a. Complete the sections of the HAWB that have not been pre-printed
    b. Affix the HAWB to the exterior of the shipper. This form is an internal tracking form used by World to identify your shipment from pick-up to delivery. When inquiring about your shipment, reference the waybill number in the top right hand corner. World Courier will provide these forms to you with shipper and consignee information pre-printed.
    c. World will send you an example Customs Invoice. Copy this invoice to your letterhead, fill in information for the Date, Shipper, Consignee, and estimate the amount of sample contained in the shipment (in mL) and sign.
    d. Affix the Customs Invoice to the shipper exterior.
    e. Along with the documents listed above, also give the signed Declaration Statement to the World Courier person picking up the shipment.
11. Call World Courier Services to arrange for pick-up:
    - Finland: 9 8700 3300
    - Germany: 89 9698 9290
    - Sweden: 8 59441 480

    You will need to provide the following information to the World Courier Representative:
    - DCC Account Number: 10848

- Time of Pick-up
- Specification of types of samples being sent
- Number and type of boxes being shipped
- Special Instructions: Diagnostic shipment.

12. Notify the repository by email (BIO-NIDDKRepository@FisherSci.com) of an incoming shipment on the day the package is picked up by World Courier. Provide the tracking number, so the repository may track the shipment if it is delayed.

14.1.8.2. Blood samples shipped to the Autoantibody Reference Labs

Entering information into the "Sample Shipment System":

Once every two weeks the clinical centers located in the United States will send bulk shipments of serum samples for autoantibodies to the Barbara Davis Center for Childhood Diabetes; once every two weeks the clinical centers located in Europe will send bulk shipments of serum samples for autoantibodies to Southmead Hospital.

1. Logon to the TEDDY website, http://teddy.epi.usf.edu/
2. Go to the "Sample Shipment System" located on the left navigational toolbar under "Data Management".
3. Enter the date of shipment.
4. If you have user access to more than one shipment origin, you will need to choose which destination the samples you are shipping are being shipped from. If you only have user access to one shipment origin, the 'Origin' drop-down menu will be defaulted to that location and you do not need to do anything.
5. Choose the "Autoantibody Lab" destination option under "Select where samples will be shipped to".
6. Enter the freezer box number(s) (numbers separated by commas) that you are going to be shipping that day and click "Search".
7. The Local Code, Subject ID, Clinical Center, Test Name, Vial Barcode Number, Visit Location Code, Date Draw, Box/Pouch Number, Space Number, Sample Volume, Site Number (this will only appear for samples being shipped to the Repository) and "Delete From Shipment" option will appear for all the samples that are located in the box(es).
8. Enter the tracking number and courier service for that shipment and any comments you would like to notify the lab about.
9. Click on "Create Shipping List" "Print and Email Shipping List". A dialog box will open that asks "Are you sure you want to print and email the shipment list?" Press 'OK' if you do and 'Cancel' if you don't.

10. Once 'OK' has been clicked an Excel file will be created that will contain information pertaining to each sample (Vial Barcode Number, Subject ID, etc).
11. Save this file for your records; an email containing this file will automatically be sent to the DCC and to the Autoantibody Reference Lab.
12. Print out a copy of this list to be shipped with the samples.
13. Repeat this process as necessary until all the boxes you will be sending that day have been entered.

Packing and Shipping Instructions for all Sites:

1. Place the freezer box along with a STP-152 absorbent strip inside a STP-731 inner leak proof poly (plastic) bag. Seal the bag.
2. Place the poly bag inside a STP-730 envelope, fold over and tuck the STP-730 into pocket.
3. Place the STP-730 envelope in the center of the STP-309 shipper.
4. Fill the remainder of the space between the STP-730 envelope and the inner walls of the cooler with dry ice.
5. Put the lid on the cooler and place the excel printout (containing the sample information) on top of the cooler. Place the "empty packaging cover" (if included – this will be one piece of cardboard that is attached to the outside of the box) on top of the list.
6. Close and tape the outer cardboard box.
7. Attach labels to side of box with "Biological Products Diagnostic Specimens" statement:
    a. Stick the dry ice label in the upper left corner. Enter the weight of dry ice in kg on the label.
    b. Stick a separate address label in the lower left corner under the dry ice label.
    c. Don't cover the words "Diagnostic Specimens"

    If shipping to the United States Autoantibody Lab the address should read:

    Barbara Davis Center for Childhood Diabetes
    Attn: Liping Yu (TEDDY Study)
    M20-4201E
    1775 Aurora Ct, UC Denver, AMC
    Aurora, CO 80045
    USA

    If shipping to the European Autoantibody Lab the address should read:

    Kyla Chandler (TEDDY Study)
    University of Bristol

Diabetes and Metabolism
Learning and Research Building
Southmead Hospital
Bristol, BS10 5NB
United Kingdom

8. **<u>For shipments within the United States</u>** use the pre-printed FedEx US air bill provided to you to ship the specimens to the Barbara Davis Center for Childhood Diabetes.
    a. In Section 1, enter the date, your name and phone number. (Sender's FedEx Account Number, Company and Address information should be already pre-printed on the air bill).
    b. Section 3, should already be pre-printed on the air bill with the US Autoantibody Lab address

    Barbara Davis Center for Childhood Diabetes
    Attn: Liping Yu (TEDDY Study)
    M20-4201E
    1775 Aurora Ct, UC Denver, AMC
    Aurora, CO 80045
    USA

    c. Under Section 4a, Express Package Service, mark "FedEx Standard Overnight".
    d. Complete Section 5, Packaging
    e. Complete Section 6, Special Handling:
        i. Under "Does this shipment contain dangerous goods?" check "Yes, Shippers Declaration not required".
        ii. Check the "Dry Ice" block and enter "1" x "#" kg. This is the total weight of dry ice added to the shipping box, in kg.
    f. Under Section 7, Payment:
        i."Sender" should be pre-marked (DCC account information is listed on the Sender section)
        ii.Enter "1" under "Total Packages".
        iii.Weigh the package and indicate the weight of the package under "Total Weight"
    g. Follow the peel and stick instructions on the back of the air bill (no document holder required).
    h. Attach the air bill to the lower right corner of the side of the box.
    i. Call FedEx at 1.800.Go.FedEx® (800.463.3339) or go to http://www.fedex.com/us/ to schedule a pick-up
    j. Attach "Biological Substance Category B" label to one side of shipping box.

k. Fill out "Dry Ice" label and attach to one side of shipping box – include dry ice weight (kg), ship to and ship from information.

9. **For shipments within Europe** use the preprinted World House Air Way Bill (HAWB) to ship the samples to Southmead Hospital. **PLEASE DO NOT SEND SHIPMENTS ON THURSDAY OR FRIDAY IN ORDER TO AVOID THAWING OF SAMPLES OVER THE WEEKEND.**

   Note: Some TEDDY European sites may choose to use TNT Courier services instead of World Courier services to ship the Autoantibody Reference Lab samples to Southmead Hospital.

   a. Complete the sections of the HAWB that have not been pre-printed
   b. Affix the HAWB to the exterior of the shipper. This form is an internal tracking form used by World to identify your shipment from pick-up to delivery. When inquiring about your shipment, reference the waybill number in the top right hand corner. World Courier will provide these forms to you with shipper and consignee information pre-printed.
   c. World will send you an example Customs Invoice, you need to copy this invoice to your letterhead, fill in information for the Date, Shipper, Consignee, and estimate the amount of sample contained in the shipment (in mL) and sign.
   d. Affix the Customs Invoice to the shipper exterior.
   e. Along with the documents listed above, also give the signed Declaration Statement to the World Courier person picking up the shipment.
   f. Call World Courier Services to arrange for pick-up:
      - Finland: 9 8700 3300
      - Germany: 89 9698 9290
      - Sweden: 8 59441 480
   g. You will need to provide the following information to the World Courier Representative:
      - DCC Account Number: 10848
      - Time of Pick-up
      - Specification of types of samples being sent
      - Number and type of boxes being shipped
      - Special Instructions: Diagnostic shipment

14.1.8.3. Blood samples shipped to the HLA Reference Lab

Entering information into the "Sample Shipment System":

Once a month the clinical centers will send bulk shipments of whole blood samples to the Children's Hospital & Research Center Oakland (this whole blood sample will be drawn from the child at the 6, 9, 12 or 15 month clinic visit. Sites are encouraged to complete this collection by the earliest visit with a full volume blood draw, but in all cases by the 15 month visit).

1. Logon to the TEDDY website, http://teddy.epi.usf.edu/
2. Go to the "Sample Shipment System" located on the left navigational toolbar under "Data Management".
3. Enter the date of shipment.
4. If you have user access to more than one shipment origin, you will need to choose which destination the samples you are shipping are being shipped from. If you only have user access to one shipment origin, the 'Origin' drop-down menu will be defaulted to that location and you do not need to do anything.
5. Choose the "HLA Reference Lab" destination option under "Select where samples will be shipped to".
6. Enter the freezer box number(s) (numbers separated by commas) that you are going to be shipping that day and click "Search".
7. The Local Code, Subject ID, Clinical Center, Test Name, Vial Barcode Number, Visit Location Code, Date Draw, Box/Pouch Number, Space Number, Sample Volume, Site Number (this will only appear for samples being shipped to the Repository) and "Delete From Shipment" option will appear for all the samples that are located in the box(es).
8. Enter the tracking number and courier service for that shipment and any comments you would like to notify the lab about.
9. Click on "Print and Email Shipping List". A dialog box will open that asks "Are you sure you want to print and email the shipment list?" Press 'OK' if you do and 'Cancel' if you don't.
10. Once 'OK' has been clicked an Excel file will be created that will contain information pertaining to each sample (Vial Barcode Number, Subject ID, etc).
11. Save this file for your records; an email containing this file will automatically be sent to the DCC and to the HLA Reference Lab.
12. Print out a copy of this list to be shipped with the samples.
13. Repeat this process as necessary until all the boxes you will be sending that day have been entered.

Packing and Shipping Instructions for all sites:

1. Place the freezer box along with a STP-152 absorbent strip inside a STP-731 inner leak proof poly (plastic) bag. Seal the bag.
2. Place the poly bag inside a STP-730 envelope, fold over and tuck the STP-730 into pocket.
3. Place the STP-730 envelope in the center of the STP-309 shipper.
4. Fill the remainder of the space between the STP-730 envelope and the inner walls of the cooler with dry ice.
5. Put the lid on the cooler and place the excel printout (containing the specimen information) on top of the cooler. Place the "empty packaging cover" (if included – this will be one piece of cardboard that is attached to the outside of the box) on top of the list.
6. Close and tape the outer cardboard box.
7. Attach labels to side of box with "Biological Products Diagnostic Specimens" statement:
   a. Stick the dry ice label in the upper left corner. Enter the weight of dry ice in kg on the label.
   b. Stick a separate address label in the lower left corner under the dry ice label that should read:

      PNDRI
      Attention: Michael Killian
      720 Broadway
      Seattle, WA 98122
      mkillian@prni@org

8. **For shipments within the United States** use the pre-printed FedEx US air bill provided to you to ship the specimens to Children's Hospital & Research Center Oakland
   a. In Section 1, enter the date, your name and phone number. (Sender's FedEx Account Number, Company and Address information should be already pre-printed on the air bill).
   b. Section 3, should already be pre-printed on the air bill with the Children's Hospital & Research Center Oakland's address.

      PNDRI
      Attention: Michael Killian
      720 Broadway
      Seattle, WA 98122
      mkillian@prni@org

c. Under Section 4a, Express Package Service, mark "FedEx Standard Overnight".
d. Complete Section 5, Packaging
e. Complete Section 6, Special Handling:
    i. Under "Does this shipment contain dangerous goods?" check "Yes, Shippers Declaration not required".
e. Under Section 7, Payment:
    i. "Sender" should be pre-marked (DCC account information is listed in the Sender section).
    ii. Fill in the FedEx Account Number.
    iii. Enter "1" under "Total Packages".
    iv. Weigh the package and indicate the weight of the package under "Total Weight"
    v. Follow the peel and stick instructions on the back of the air bill (no document holder required).
f. Attach the air bill to the lower right corner.
g. Call FedEx at 1.800.Go.FedEx® (800.463.3339) or go to http://www.fedex.com/us/ to schedule a pick-up
h. Attach "Biological Substance Category B" label to one side of shipping box.
i. Fill out "Dry Ice" label and attach to one side of shipping box – include dry ice weight (kg), ship to and ship from information.

9. **For shipments from Europe to the US** use the preprinted World House Air Way Bill (HAWB) to ship the samples to Children's Hospital & Research Center Oakland
    a. Complete the sections of the HAWB that have not been pre-printed
    b. Affix the HAWB to the exterior of the shipper. This form is an internal tracking form used by World to identify your shipment from pick-up to delivery. When inquiring about your shipment, reference the waybill number in the top right hand corner. World Courier will provide these forms to you with shipper and consignee information pre-printed.
    c. World will send you an example Customs Invoice, you need to copy this invoice to your letterhead, fill in information for the Date, Shipper, Consignee, and estimate the amount of sample contained in the shipment (in mL) and sign.
    d. Affix the Customs Invoice to the shipper exterior
    e. Along with the documents listed above, also give the signed Declaration Statement to the World Courier person picking up the shipment.
    f. Call World Courier Services to arrange for pick-up:
        - Finland: 9 8700 3300

- Germany: 89 9698 9290
- Sweden: 8 59441 480

g. You will need to provide the following information to the World Courier Representative:
   - DCC Account Number: 10848
   - Time of Pick-up
   - Specification of types of samples being sent
   - Number and type of boxes being shipped
   - Special Instructions: Diagnostic shipment

14.1.8.4. Non-HLA genotyping samples and parent and sibling DNA samples shipped to Repository

Entering information into the "Sample Shipment System":
Clinical Centers will send bulk shipments of DNA samples to the Repository.

1. Logon to the TEDDY website, http://teddy.epi.usf.edu/
2. Go to the "Sample Shipment System" located on the left navigational toolbar under "Data Management".
3. Enter the date of shipment.
4. If you have user access to more than one shipment origin, you will need to choose which destination the samples you are shipping are being shipped from. If you only have user access to one shipment origin, the 'Origin' drop-down menu will be defaulted to that location and you do not need to do anything.
5. Choose the "Repository" destination option under "Select where samples will be shipped to".
6. Enter the box or pouch number(s) (numbers separated by commas) that you are going to be shipping that day and click "Search".
7. The Local Code, Subject ID, Clinical Center, Test Name, Vial Barcode Number, Visit Location Code, Date Draw, Box/Pouch Number, Space Number, Sample Volume, Site Number (this will only appear for samples being shipped to the Repository) and "Delete From Shipment" option will appear for all the samples that are located in the pouch(es).
8. Enter the tracking number and courier service for that shipment and any comments you would like to notify the lab about.
9. Click on "Print and Email Shipping List". A dialog box will open that asks "Are you sure you want to print and email the shipment list?" Press 'OK' if you do and 'Cancel' if you don't.
10. Once 'OK' has been clicked an Excel file will be created that will contain information pertaining to each sample (Vial Barcode Number, Subject ID, etc).
11. Save this file for your records; an email containing this file will automatically be sent to the DCC and to the Repository.

12. Print out a copy of this list to be shipped with the samples.
13. Repeat this process as necessary until all the boxes you will be sending that day have been entered.

Packing and Shipping Instructions for all sites:

1. Insert the 8 ml tubes into 3" freezer boxes.
2. **The lab has requested that you ship Monday through Tuesday** only (in order to ensure delivery prior to the weekend) by Federal Express (domestic U.S. shipments) or World Courier (international shipments) using preprinted airbills provided.
3. Place the 3" freezer box along with a STP-152 absorbent strip inside a STP-731 inner leak proof poly (plastic) bag. Seal the bag.
4. Place the poly bag inside a STP-730 envelope, fold over and tuck the STP-730 into pocket.
5. Place up to three filled STP-730 envelopes in the cardboard inner box, tape the box shut and place it in the middle of the cooler in the STP-309 shipper. If there are only one or two vial boxes in the shipment, fill the rest of the space inside the cardboard inner box with packing material (e.g. bubble wrap or newspaper) to prevent movement during shipment.
6. Put the lid on the cooler and place the excel printout (containing the sample information) on top of the cooler. Place the "empty packaging cover" (if included – this will be one piece of cardboard that is attached to the outside of the box) on top of the list.
7. Close and tape the outer cardboard box.

For shipments within the United States: use the pre-printed FedEx US air bill provided to you to ship the specimens to the Repository.

1. In Section 1, enter the date, your name and phone number (Sender's FedEx Account Number, Company and Address information should be already pre-printed on the air bill)..
2. Section 3, should already be pre-printed on the air bill with the Repository address

Chris Deigan
Disease Prevention
Fisher BioServices
20301 Century Blvd.
Building 6, Suite 400
Germantown MD 20874

3. Under Section 4a, Express Package Service, mark "FedEx Standard Overnight".
4. Complete Section 5, Packaging.
5. Complete Section 6, Special Handling:
   a. Under "Does this shipment contain dangerous goods?" check "Yes, Shippers Declaration not required".
   b. Check the "Dry Ice" block and enter "1" x "#" kg. This is the total weight of dry ice added to the shipping box, in kg.
6. Under Section 7, Payment:
   a. "Sender" should be pre-marked (DCC account information is listed in the Sender section)
   b. Enter "1" under "Total Packages".
   c. Weigh the package and indicate the weight of the package under "Total Weight"
7. Follow the peel and stick instructions on the back of the air bill (no document holder required).
8. Attach the air bill to the lower right corner of the side of the box.
9. Call FedEx at 1.800.Go.FedEx® (800.463.3339) or go to http://www.fedex.com/us/ to schedule a pick-up
10. Attach "Biological Substance Category B" label to one side of shipping box
11. Fill out "Dry Ice" label and attach to one side of shipping box-include dry ice weight (kg), ship to and ship from information.

For shipments from Europe to the US use the preprinted World House Air Way Bill (HAWB) to ship the samples to the Repository

1. Complete the sections of the HAWB that have not been pre-printed
2. Affix the HAWB to the exterior of the shipper. This form is an internal tracking form used by World to identify your shipment from pick-up to delivery. When inquiring about your shipment, reference the waybill number in the top right hand corner. World Courier will provide these forms to you with shipper and consignee information pre-printed.
3. World will send you an example Customs Invoice, you need to copy this invoice to your letterhead, fill in information for the Date, Shipper, Consignee, and estimate the amount of sample contained in the shipment (in mL) and sign.
4. Affix the Customs Invoice to the shipper exterior
5. Along with the documents listed above, also give the signed Declaration Statement to the World Courier person picking up the shipment.

6. Call World Courier Services to arrange for pick-up:
    - Finland: 9 8700 3300
    - Germany: 89 9698 9290
    - Sweden: 8 59441 480
7. You will need to provide the following information to the World Courier Representative:
    - DCC Account Number: 10848
    - Time of Pick-up
    - Specification of types of samples being sent
    Number and type of boxes being shipped
    - Special Instructions: Diagnostic shipment

14.1.8.5. Blood samples shipped to the HbA1c Lab

Entering information into the "Sample Shipment System":
Clinical Centers will send bulk shipments of HbA1c samples to the HbA1c Lab on a quarterly basis.

1. Logon to the TEDDY website, http://teddy.epi.usf.edu/
2. Go to the "Sample Shipment System" located on the left navigational toolbar under "Data Management".
3. Enter the date of shipment.
4. If you have user access to more than one shipment origin, you will need to choose which destination the samples you are shipping are being shipped from. If you only have user access to one shipment origin, the 'Origin' drop-down menu will be defaulted to that location and you do not need to do anything.
5. Choose the "HbA1c Lab" destination option under "Select where samples will be shipped to".
6. Enter the box number(s) (numbers separated by commas) that you are going to be shipping that day and click "Search".
7. The Local Code, Subject ID, Clinical Center, Test Name, Vial Barcode Number, Visit Location Code, Date Draw, Box/Pouch Number, Space Number, Sample Volume, Site Number (this will only appear for samples being shipped to the Repository) and "Delete From Shipment" option will appear for all the samples that are located in the box(es).
8. Enter the tracking number and courier service for that shipment and any comments you would like to notify the lab about.
9. Click on "Print and Email Shipping List". A dialog box will open that asks "Are you sure you want to print and email the shipment list?" Press 'OK' if you do and 'Cancel' if you don't.
10. Once 'OK' has been clicked an Excel file will be created that will contain information pertaining to each sample (Vial Barcode Number, Subject ID, etc).

11. Save this file for your records; an email containing this file will automatically be sent to the DCC and to the HbA1c Lab.
12. Print out a copy of this list to be shipped with the samples.
13. Repeat this process as necessary until all the boxes you will be sending that day have been entered.

Packing and Shipping Instructions for US Sites:

1. Place the 2" freezer box along with a STP-152 absorbent strip inside a STP-731 inner leak proof poly (plastic) bag. Seal the bag.
2. Place the poly bag inside a STP-730 envelope, fold over and tuck the STP-730 into pocket.
3. Place up to three filled STP-730 envelopes in the cardboard inner box, tape the box shut and place it in the middle of the cooler in the STP-309 shipper. If there are only one or two vial boxes in the shipment, fill the rest of the space inside the cardboard inner box with packing material (e.g. bubble wrap or newspaper) to prevent movement during shipment.
4. Fill the remainder of the space between the cardboard box and the inner walls of the cooler with dry ice.
5. Put the lid on the cooler and place the excel printout (containing the sample information) on top of the cooler. Place the "empty packaging cover" (if included – this will be one piece of cardboard that is attached to the outside of the box) on top of the list.
6. Close and tape the outer cardboard box.
7. Attach labels to side of box with "Biological Products Diagnostic Specimens" statement:
   a. Stick the dry ice label in the upper left corner. Enter the weight of dry ice in kg on the label.
   b. Stick a separate address label in the lower left corner, under the dry ice label, that reads:

Rick Sanchegraw
University of Mo-Columbia
1 Hospital Dr. Rm M767A
Columbia, MO 65212
Phone (573) 882-0981
sanchegrawr@health.missouri.edu

   c. Stick the "UN3373 Diagnostic Specimens" label to the right of the dry ice label.
   d. Attach "Biological Substance Category B" label to one side of shipping box.

8. use the pre-printed FedEx US air bill provided to you to ship the specimens to the HbA1c lab.

h. In Section 1, enter the date, your name and phone number. (Sender's FedEx Account Number, Company and Address information should be already pre-printed on the air bill).
i. Section 3, should already be pre-printed on the air bill with the HbA1c Lab address

Rick Sanchegraw
University of Mo-Columbia
1 Hospital Dr. Rm M767A
Columbia, MO 65212
Phone (573) 882-0981
sanchegrawr@health.missouri.edu

j. Under Section 4a, Express Package Service, mark "FedEx Standard Overnight".
k. Complete Section 5, Packaging
l. Complete Section 6, Special Handling:
   iii. Under "Does this shipment contain dangerous goods?" check "Yes, Shippers Declaration not required".
   iv. Check the "Dry Ice" block and enter "1" x "#" kg. This is the total weight of dry ice added to the shipping box, in kg.
m. Under Section 7, Payment:
   i."Sender" should be pre-marked (DCC account information is listed on the Sender section)
   ii.Enter "1" under "Total Packages".
   iii.Weigh the package and indicate the weight of the package under "Total Weight"
n. Follow the peel and stick instructions on the back of the air bill (no document holder required).
o. Attach the air bill to the lower right corner of the side of the box.
p. Call FedEx at 1.800.Go.FedEx® (800.463.3339) or go to http://www.fedex.com/us/ to schedule a pick-up
q. Attach "Biological Substance Category B" label to one side of shipping box.
r. Fill out "Dry Ice" label and attach to one side of shipping box – include dry ice weight (kg), ship to and ship from information.

Packing and Shipping Instructions for European Sites:

1. Place the 2" freezer box along with an absorbent strip inside the inner leak proof poly (plastic) bag. Seal the bag.
2. Place the plastic bag inside the long Tyvek envelope. Place the box inside the far end of the long pocket of the envelope. Crease the envelope near the middle, fold the envelope over, and place the end of

the envelope containing the box inside the short pocket on the opposite side of the envelope. Push the box firmly into the short end of the envelope.

3. Put a layer of dry ice in the bottom of the box. Place the Tyvek envelopes containing boxes on the dry ice.
4. Fill the remainder of the space in the shipper with dry ice.
5. Put the foam insert, or lid, on top of the dry ice in the opening. Place a copy of the manifest shipping form inside a zip-lock bag, and set it on top of the foam insert under the lid flaps.
6. Close and tape the cardboard box.
7. Use the preprinted World House Air Way Bill (HAWB) to ship the samples to the HbA1c Lab at the address below:

Rick Sanchegraw
University of Mo-Columbia
1 Hospital Dr. Rm M767A
Columbia, MO 65212
Phone (573) 882-0981
sanchegrawr@health.missouri.edu

a. Complete the sections of the HAWB that have not been pre-printed
b. Affix the HAWB to the exterior of the shipper. This form is an internal tracking form used by World to identify your shipment from pick-up to delivery. When inquiring about your shipment, reference the waybill number in the top right hand corner. World Courier will provide these forms to you with shipper and consignee information pre-printed.
c. World will send you an example Customs Invoice, you need to copy this invoice to your letterhead, fill in information for the Date, Shipper, Consignee, and estimate the amount of sample contained in the shipment (in mL) and sign.
d. Affix the Customs Invoice to the shipper exterior
e. Along with the documents listed above, also give the signed Declaration Statement to the World Courier person picking up the shipment.
f. Call World Courier Services to arrange for pick-up:
    - Finland: 9 8700 3300
    - Germany: 89 9698 9290
    - Sweden: 8 59441 480
g. You will need to provide the following information to the World Courier Representative:
    - DCC Account Number: 10848
    - Time of Pick-up
    - Specification of types of samples being sent

- Number and type of boxes being shipped
- Special Instructions: Diagnostic shipment

14.1.8.6. Blood samples shipped to the Thyroid Lab

Entering information into the "Sample Shipment System":
Clinical Centers will send bulk shipments of Thyroid samples to the Thyroid Lab every two weeks. **NOTE: these samples must be shipped to the Thyroid lab within 2 weeks of collection as TSH is only stable for 1 month.** Please only ship to the lab Monday – Wednesday.

1. Logon to the TEDDY website, http://teddy.epi.usf.edu/
2. Go to the "Sample Shipment System" located on the left navigational toolbar under "Data Management".
3. Enter the date of shipment.
4. If you have user access to more than one shipment origin, you will need to choose which destination the samples you are shipping are being shipped from. If you only have user access to one shipment origin, the 'Origin' drop-down menu will be defaulted to that location and you do not need to do anything.
5. Choose the "Thyroid Lab" destination option under "Select where samples will be shipped to".
6. Enter the box number(s) (numbers separated by commas) that you are going to be shipping that day and click "Search".
7. The Local Code, Subject ID, Clinical Center, Test Name, Vial Barcode Number, Visit Location Code, Date Draw, Box/Pouch Number, Space Number, Sample Volume and "Delete From Shipment" option will appear for all the samples that are located in the box(es).
8. Enter the tracking number and courier service for that shipment and any comments you would like to notify the lab about.
9. Click on "Print and Email Shipping List". A dialog box will open that asks "Are you sure you want to print and email the shipment list?" Press 'OK' if you do and 'Cancel' if you don't.
10. Once 'OK' has been clicked an Excel file will be created that will contain information pertaining to each sample (Vial Barcode Number, Subject ID, etc).
11. Save this file for your records; an email containing this file will automatically be sent to the DCC and to the HbA1c Lab.
12. Print out a copy of this list to be shipped with the samples.
13. Repeat this process as necessary until all the boxes you will be sending that day have been entered.

Packing and Shipping Instructions for US Sites:

1. Place the 2" freezer box along with a STP-152 absorbent strip inside a STP-731 inner leak proof poly (plastic) bag. Seal the bag.
   NOTE: Since TEDDY is using the same lab for OGTT and Thyroid antibody analyses, OGTT samples and Thyroid samples can be shipped together to the lab (in different freezer boxes). Please make sure that each freezer box is labeled either "OGTT" or "Thyroid".
2. Place the poly bag inside a STP-730 envelope, fold over and tuck the STP-730 into pocket.
3. Place up to three filled STP-730 envelopes in the cardboard inner box, tape the box shut and place it in the middle of the cooler in the STP-309 shipper. If there are only one or two vial boxes in the shipment, fill the rest of the space inside the cardboard inner box with packing material (e.g. bubble wrap or newspaper) to prevent movement during shipment.
4. Fill the remainder of the space between the cardboard box and the inner walls of the cooler with dry ice.
5. Put the lid on the cooler and place the excel printout (containing the sample information) on top of the cooler. Place the "empty packaging cover" (if included – this will be one piece of cardboard that is attached to the outside of the box) on top of the list.
6. Close and tape the outer cardboard box.
7. Attach labels to side of box with "Biological Products Diagnostic Specimens" statement:
   a. Stick the dry ice label in the upper left corner. Enter the weight of dry ice in kg on the label.
   b. Stick a separate address label in the lower left corner, under the dry ice label, that reads:

UFHPL Endocrine Lab
ATTN: Dave Pittman
4800 SW 35 Drive
Gainesville, FL 32608
(352) 265-9900
UF_TEDDY@Pathology.ufl.edu

   c. Stick the "UN3373 Diagnostic Specimens" label to the right of the dry ice label.
   d. Attach "Biological Substance Category B" label to one side of shipping box.
8. Use the pre-printed FedEx US air bill provided to you to ship the specimens to the Thyroid lab.
   a. In Section 1, enter the date, your name and phone number. (Sender's FedEx Account Number, Company

and Address information should be already pre-printed on the air bill).

b. Section 3, should already be pre-printed on the air bill with the Thyroid Lab address

UFHPL Endocrine Lab
ATTN: Dave Pittman
4800 SW 35 Drive
Gainesville, FL 32608
(352) 265-9900
UF_TEDDY@Pathology.ufl.edu

c. Under Section 4a, Express Package Service, mark "FedEx Standard Overnight".
d. Complete Section 5, Packaging
e. Complete Section 6, Special Handling:
f. Under "Does this shipment contain dangerous goods?" check "Yes, Shippers Declaration not required".
g. Check the "Dry Ice" block and enter "1" x "#" kg. This is the total weight of dry ice added to the shipping box, in kg.
h. Under Section 7, Payment:
   a. "Sender" should be pre-marked (DCC account information is listed on the Sender section
i. Enter "1" under "Total Packages".
j. Weigh the package and indicate the weight of the package under "Total Weight"
k. Follow the peel and stick instructions on the back of the air bill (no document holder required).
l. Attach the air bill to the lower right corner of the side of the box.
m. Call FedEx at 1.800.Go.FedEx® (800.463.3339) or go to http://www.fedex.com/us/ to schedule a pick-up
n. Attach "Biological Substance Category B" label to one side of shipping box.
o. Fill out "Dry Ice" label and attach to one side of shipping box – include dry ice weight (kg), ship to and ship from information.

Packing and Shipping Instructions for European Sites:

1. Place the 2" freezer box along with an absorbent strip inside the inner leak proof poly (plastic) bag. Seal the bag.
   NOTE: Since TEDDY is using the same lab for OGTT and Thyroid antibody analyses, OGTT samples and Thyroid samples can be shipped together to the lab (in different

freezer boxes). Please make sure that each freezer box is labeled either "OGTT" or "Thyroid".

2. Place the plastic bag inside the long Tyvek envelope. Place the box inside the far end of the long pocket of the envelope. Crease the envelope near the middle, fold the envelope over, and place the end of the envelope containing the box inside the short pocket on the opposite side of the envelope. Push the box firmly into the short end of the envelope.
3. Put a layer of dry ice in the bottom of the box. Place the Tyvek envelopes containing boxes on the dry ice.
4. Fill the remainder of the space in the shipper with dry ice.
5. Put the foam insert, or lid, on top of the dry ice in the opening. Place a copy of the manifest shipping form inside a zip-lock bag, and set it on top of the foam insert under the lid flaps.
6. Close and tape the cardboard box.
7. Use the preprinted World House Air Way Bill (HAWB) to ship the samples to the Thyroid Lab at the address below:

UFHPL Endocrine Lab
ATTN: Dave Pittman
4800 SW 35 Drive
Gainesville, FL 32608
(352) 265-9900
USA
UF_TEDDY@Pathology.ufl.edu

a. Complete the sections of the HAWB that have not been pre-printed
b. Affix the HAWB to the exterior of the shipper. This form is an internal tracking form used by World to identify your shipment from pick-up to delivery. When inquiring about your shipment, reference the waybill number in the top right hand corner. World Courier will provide these forms to you with shipper and consignee information pre-printed.
c. World will send you an example Customs Invoice, you need to copy this invoice to your letterhead, fill in information for the Date, Shipper, Consignee, and estimate the amount of sample contained in the shipment (in mL) and sign.
d. Affix the Customs Invoice to the shipper exterior
e. Along with the documents listed above, also give the signed Declaration Statement to the World Courier person picking up the shipment.
f. Call World Courier Services to arrange for pick-up:
   - Finland: 9 8700 3300

- Germany: 89 9698 9290
- Sweden: 8 59441 480

g. You will need to provide the following information to the World Courier Representative:
   - DCC Account Number: 10848
   - Time of Pick-up
   - Specification of types of samples being sent
   - Number and type of boxes being shipped
   - Special Instructions: Diagnostic shipment

Section 14 Appendix

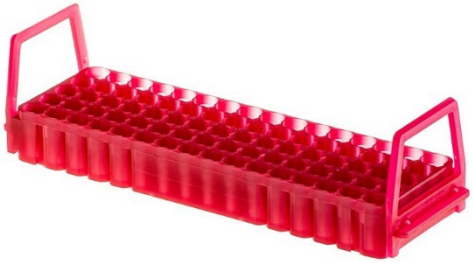
A. Autoclave Sterilization of Etched Amber Tubes – Instructions for Clinical Centers

Autoclave Sterilization of Etched Amber Tubes – Instructions for Clinical Centers

The amber vials for light sensitive sample storage will be sent to the clinical centers after they have been etched with unique barcodes. Clinical centers will need to autoclave the tubes and caps to sterilize them before use.

The etched tubes will arrive at the clinical centers in bags. The caps will be packaged separately.

- Remove the tubes and caps from the plastic bags before autoclaving them- the bags will melt in the autoclave!
- Place the tubes in an autoclave-safe rack, that will hold them upright, like this one:



- LOOSELY place the caps on top of the tubes, but do not screw the caps down onto the threads.
- Autoclave the racks of loosely capped tubes in a standard autoclave at 121°C, 15psig (1bar) for a minimum of 20 minutes.
- After the cycle is complete, allow the racks of tubes to cool completely to room temperature, then tighten the caps down onto the threads. Do not tighten the caps before the tubes reach room temperature.
- Capped tubes are now sterile, and the red or blue stickers can be applied to the caps.

The color-coded sterile tubes can be stored as other TEDDY tubes are, un

15. Stool Sample

NOTE: In August 2018 all stool sample collections were stopped on all subjects. Stool sample collection compliance was less than 20% in Europe and 15% in the US. The small numbers did not warrant the cost of collection, processing, nor the burden on the families.

15.1. Frequently Asked Questions: Stool Sample Collection

- If you cannot obtain enough stool sample from a single diaper can it be collected from multiple diapers throughout a day? – *YES*
- If collected from multiple diapers, how should samples be stored in between collections (refrigerated or at room temperature)? *REFRIGERATION WOULD BE OPTIMAL, BUT IF THIS IS NOT POSSIBLE THEN ROOM TEMPERATURE IS OKAY.*
- If there is only enough stool sample for one full tube, is it better to fill one tube full or fill two tubes half-full? *TWO HALF-FULL TUBES IS BEST*
- Is it okay to collect stool samples from different parts of the diaper? *YES*
- How should the stool be stored before mailing (if for example they collect the sample at night and cannot mail it until the next morning)? *REFRIGERATION WOULD BE OPTIMAL, BUT IF THIS IS NOT POSSIBLE THEN ROOM TEMPERATURE IS OKAY.*
- Should the stool sample be collected from different parts of the diaper? *IT DOES NOT MATTER IF THE SAMPLE IS TAKEN FROM A SINGLE SITE OR MULITPLE SITES OF THE DIAPER.*
- Once families begin to collect stool samples only every 3 months (which occurs after 48 months of age until 10 years of age) and every 6 months (which occurs from age 10 years through the end of the study) instead of monthly, should families be provided with a suggested collection time period? *PARENTS SHOULD TRY TO COLLECT THE STOOL SAMPLE WITHIN A WEEK OF THE SCHEDULED TEDDY VISIT.*
- How long can family keep a stool sample before mailing it? *IT'S ALWAYS BEST FOR THE FAMILY TO MAIL OUT THE STOOL SAMPLE AS SOON AFTER COLLECTING IT AS POSSIBLE, BUT SOMETIMES, A SAMPLE MAY BE COLLECTED AFTER THE MAIL HAS GONE OUT OR OVER A WEEKEND. KEEPING A STOOL SAMPLE IN THE REFRIGERATOR FOR 2 TO 3 DAYS BEFORE MAILING IT IS FINE, BUT IT SHOULD NOT BE FROZEN.*

15.2. Stool Sample Collection

The child's parent(s) will collect at least 5g of the child's stool each month up until 48 months of age, then every three months until the age of 10 years and then biannually thereafter into the three plastic stool containers provided by the clinical center. The TEDDY study group has adopted a compromise position that *promotes* stool sample collection 4 times a year for children who are antibody positive and *encourages* stool sample collection 4 times a year for children who are antibody

negative, after age 4. The difference in approach is that children who are antibody positive are, according to the current protocol, on a 4 times per year follow up schedule which makes the increased frequency of stool sample collection consistent with their increased surveillance schedule (visits and blood draws). For antibody negative children, those who are willing to submit stool samples will be asked to continue on the more frequent schedule (which may actually increase compliance) while others who do not will not be considered as non compliant.

Rectal swab collection will be an optional collection method for non-compliant subjects who are less than four years of age; the rectal swab collection will occur in the TEDDY clinic by the study nurse.

Some parents who have toilet trained their children say that the child will not use the bowl TEDDY offers to collect the sample. For these parents, sites can give the parents an option of using cotton swabs (provided by the site in the collection kit) for the stool collection when helping the child wipe.

15.3. Stool Sample Collection Kits

The stool sample collection kits will be assembled at each of the clinical centers and given out to the families for them to use at home. Each kit contains the necessary items for the collection of a one month stool sample:

All sites:
1. 3 etched stool collection tubes (3 outer tubes, 3 inner tubes, 3 lids)
2. 1 pair of Gloves (varies by site; clinical center must provide)
3. "Instructions on how to collect poop sample" Sheet (with subject ID and local code indicated on sheet)

US sites:
1. 1 STP 701 Saf T Pak leak proof clear bag
2. 1 absorbent strip
3. 1 STP 700 Saf T Pak white envelope
4. 1 US Post Office Express Mail mailing label

   For ambient shipping (during winter months)*:
   1. 1 cardboard shipper

   For refrigerated shipping (during summer months)*:
   1. 1 Styrofoam container
   2. 1 cardboard shipper
   3. 3 gel packs (one 3 oz, two 8 oz)

European sites:
1. 1 leak proof clear bag
2. 1 absorbent pad
3. 1 gel pack
4. 1 cardboard shipper from Mekalasi

*The determination of which months are considered to be 'winter' and 'summer' months is left up to the individual clinical center to decide. Months designated by US clinical centers as 'summer' months (list subject to change):

- Colorado: May 1 – September 30
- Georgia/Florida: May 1 – September 30
- Washington: June 1 – September 30

15.3.1. Optional Rectal Swab Collection for Non-compliant Subjects Less than Four Years of Age

Rectal swab collection will be an optional collection method for non-compliant subjects who are less than four years of age; the rectal swab collection will occur in the TEDDY clinic by the study nurse.

Supplies:

8ml TEDDY etched stool sample vials (no inner stool tube)
3ml Remel Microtest M4 Transport Media R12500 (per sample)
Copan Rectal Swab
3" freezer storage box, with 6x6 cell insert

Preparation for Sample Collection:

Transfer 3ml transport media into an 8ml etched stool sample vial. Media can be stored frozen at -20˚C for several months. Media can be stored at 4˚C for several weeks.

Sample Collection, Storage and Shipment:

1. Pull stool vial with media from freezer to thaw 30 minutes before visit or from refrigerator at time of visit.
2. Explain the procedure to subject and family.
   Script: *We understand that stool sample collection is sometimes hard for families. We are looking for another method that we could do here in clinic. This is similar to taking a rectal temperature, but it will be much quicker and very easy. You will be reimbursed the same as if you sent in a stool sample. Would you be willing to have us collect this sample in clinic today and at future visits instead of sending a stool sample in the mail?*
3. Wash hands and put on a pair of disposable gloves.
4. Open the peel pouch and have the swab in hand. Do not open the tube of media until after the specimen is obtained. Be careful not to allow the swab to come into contact with anything other than the child's rectum. If the swab is dropped or grabbed by the child, start with a new swab.

5. **For an infant:**
    a. Have parent lie child in supine position on cushioned exam table.
    b. Have parents remove diaper and lift child's legs exposing rectum.
    c. Use sterile cotton tipped applicator, gently swab rectal area try to obtain small amount of fecal material. If no fecal material present, gently insert tip of cotton tipped applicator into rectal opening no more than the length of the cotton on the applicator.
6. **For a child:**
    a. Have child lie prone over parents lap.
    b. Have parents gently expose buttocks.
    c. Verbally notify child of every step taken prior to touching them.
    d. Spread buttocks apart exposing rectum.
    e. Gently wipe rectal area with sterile cotton applicator, try to obtain fecal material. If no fecal material present, gently insert tip of cotton tipped applicator into the rectum no farther than the length of the cotton covering
7. Remove the top from the etched stool tube (be careful not to spill the liquid media).
8. Put the swab into the tube, rotate in the viral media and break off at the lower break point on the end opposite the swab so it fits into the tube.
9. Close the cap of the tube.
10. The end of the swab shaft may or may not insert into the cap, do not worry about this as long as the tube is securely closed.
11. Enter the stool vial information onto the subject's Stool Sample Collection Form by following the instructions in section 15.3.
12. Both European and US sites should use the "European Stool Sample System and Rectal Swab Sample System" to submit the box number, space number, date sample was received at Clinical Center and date of collection by following the instructions in section 15.3.1.
13. The vial should then be stored in a 3" freezer box with a 36 cell divider insert at -70˚C. When the sample is ready to be shipped to the Repository sites should use the Sample Shipment System by following the instructions in section 15.6.2 and then ship the samples to the Repository.

15.4. Stool Sample Collection Forms

The SCFs contain constraints that prevent a vial barcode number from being saved more than once. If you try to save a vial barcode number that has already been saved, an error message will appear that explains why the new information cannot be saved. If the vial barcode number that you are trying to save is correct and the same vial barcode number has been entered (and saved) incorrectly for a subject that is within your clinical center, please try to determine the mistake that was made and correct appropriately on the TEDDY website (the Local Code, Subject ID, Visit Name and Test Name associated with the other sample will be provided in the error message) – if you are unable to make the correction yourself contact the DCC at

TEDDY@epi.usf.edu to make the correction for you. If the sample has already been sent to the Repository or Lab, please contact the Repository or Lab and the DCC with the correct information; once the Repository or Lab verifies that the new information you have given is correct then you should correct this information on the TEDDY website – if you are unable to make the correction yourself contact the DCC at TEDDY@epi.usf.edu to make the correction for you. If the vial barcode number was incorrectly entered and saved for a subject that is not within your clinical center, please contact the DCC at TEDDY@epi.usf.edu

There are two ways to retrieve the subject's Stool Sample Collection Form:

"Sample Collection Form" link

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Sample Collection Form" link under "Data Management" on the left navigational toolbar.
3. Enter both the Subject ID and Local Code of the subject, click "Search".
4. There is no need to select a visit for the Stool SCF (in Step 2); the Stool SCF is not visit specific. There is only one Stool SCF that is used for the purpose of entering the stool vial barcode numbers.
5. Select the desired sample collection form (e.g. Stool Sample).
6. Subject ID, Local Code, and Clinical Center fields will be prepopulated on the Sample Collection Form.
7. If subject's stool samples are collected using the toilet sample collection device (stool samples are no longer being collected from a diaper) enter the date that the subject's stool samples started being collected using the toilet sample collection device, if this date has not yet been submitted for the subject.
8. Choose the correct Visit Location Code from the drop down menu - this is the location where the TEDDY visit took place. Drop-down list based upon TEDDY Clinical Center field..
9. Place cursor in the box for 'Kit 1, Stool Sample Tube # 1', (for the next tube proceed to 'Kit 1, Stool Sample Tube #2'and so on).
10. Scan the preprinted barcode located on one of the stool tubes.
11. Repeat steps 8 and 9 as necessary.
12. Click the "Save Form" button, if the form was saved you will see "Form successfully saved" on the screen.
13. There is a data field at the bottom of the SCF to enter "Express Mail Label Numbers" associated with the subject, if the site would like to do so (this is for local site use only, the DCC does not need this information).
    a) Enter the number in the data field next to the "Add" button in the box entitled "Express Mail Label Numbers" and then press "Add"
    b) The number will be saved in the data box directly below.
14. Print the parent instructions (1 for each kit for that child) by selecting the specific instructions needed from the drop-down menu under "Print Shipment Instructions to Parents" at the top right of the screen.
15. Click the "Close Form" button.

"Enter/Edit/View" Link

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject by entering one of the following: 1) Local Code and Subject ID 2) Local Code and Date of Birth 3) Date of Birth Range 4) Clinical Center and Subject ID 5) Clinical Center and Local Code or 6) Clinical Center and/or Visit Location Code.
4. Under "Search Results", click on the Local Code of the desired subject.
5. Choose the desired Sample Collection Form by clicking on the links under "Event Title" (e.g. Stool Sample)
6. Subject ID, Local Code, and Clinical Center fields will be prepopulated on the Sample Collection Form.
7. If subject's stool samples are collected using the toilet sample collection device (stool samples are no longer being collected from a diaper) enter the date that the subject's stool samples started being collected using the toilet sample collection device, if this date has not yet been submitted for the subject.
8. Choose the correct Visit Location Code from the drop down menu - this is the location where the TEDDY visit took place. Drop-down list based upon TEDDY Clinical Center field..
9. Place cursor in the box for 'Kit 1, Stool Sample Tube # 1', (for the next tube proceed to 'Kit 1, Stool Sample Tube #2'and so on).
10. Scan the preprinted barcode located on one of the stool tubes.
11. Repeat steps 8 and 9 as necessary.
12. Click the "Save Form" button, if the form was saved you will see "Form successfully saved" on the screen.
13. There is a data field at the bottom of the SCF to enter "Express Mail Label Numbers" associated with the subject, if the site would like to do so (this is for local site use only, the DCC does not need this information).
    a) Enter the number in the data field next to the "Add" button in the box entitled "Express Mail Label Numbers" and then press "Add"
    b) The number will be saved in the data box directly below.
14. Print the parent instructions (1 for each kit for that child) by selecting the specific instructions needed from the drop-down menu under "Print Shipment Instructions to Parents" at the top right of the screen.
15. Click the "Close Form" button.

No matter which method you use to enter the stool vial barcode numbers into the stool SCF (through the "Sample Collection Form" link or the "Enter/Edit/View" link) when you open the SCF (after saving the new vial barcodes) you will see that the vial barcode numbers no longer appear in the vial barcode number/kit number table that you previously scanned them into. After the vial barcode numbers have been saved and the form has been closed, the vial barcode numbers are transferred into the table at the bottom of the form under "The following tubes have been assigned so far". This table contains:

1. Vial barcode number – this is the number that has been scanned/entered from the vial; this column contains all of the stool vials that have been assigned to this subject.
2. Date kits entered online – this is the date the vial barcode numbers were scanned into the SCF.
3. Date of collection – this is the date the stool sample was collected by the parent. For the European sites this date is entered into the "European Stool Sample System and Rectal Swab Sample System" on the TEDDY website (See MOO section 15.3.1. for instructions); for the US sites the Repository receives this information with the stool sample shipment from the parent, the date is then uploaded to the TEDDY website with the receipt confirmation file from the Repository.
4. Visit Assigned – the visit assigned column will say "Not assigned" until a date of collection is entered into the system for that particular sample. Once a date of collection has been entered the visit assigned will be populated with whichever visit window the date of collection falls into (for example Month 3).

15.3.1.European Clinical Centers and Clinical Centers Collecting Rectal Swab Samples – European Stool Sample System and Rectal Swab Sample System

TEDDY families enrolled in the study through the European sites (Germany, Finland, and Sweden) will send stool samples back to the clinical center (whereas US families will send stool samples directly to the Repository except for stool samples collected by rectal swab).

The European Clinical Centers and Clinical Centers collecting rectal swab samples will use the "European Stool Sample System and Rectal Swab Sample System" once they receive the stool samples back from the families:

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "European Stool Sample System and Rectal Swab Sample System" link under "Data Management" on the left navigational toolbar.
3. Place cursor in the "Vial Barcode Number" box.
4. Scan the preprinted barcode located on one of the stool tubes.
5. Enter the box number, space number, date sample received at clinical center and date of collection for that tube.
6. Repeat steps 3-5 as necessary.

15.5. Explanation of Stool Sample Collection to Parents/Primary Caretakers

1. As a part of the clinic visit, explain to parents why the stool samples need to be collected monthly (and then every 3 months from 48 months to 10 years of age and then every 6 months from 10 years of age through the end of the study). Be sure to include the following in your explanation:

a. The stool will be analyzed for viruses that their child may have had.
b. Not all samples will be analyzed.
c. The samples will not be done in real time, so we will not be able to provide them with the results of these tests.

2. Review sampling instructions with parents. Review these instructions, using the sample kit as a reference. (See "Poop Sample Collection Instructions" in appendix).

   US SITES: Clinic staff should verify that the correct account number, "FROM" address (clinic address not participant's home) and the correct shipping "TO" address are listed on the mailing labels prior to distributing them to the families.

   Repository address:

   Fisher Bioservices Corporation
   NIDDK Biorepository
   20301 Century Blvd.
   Building 6, Suite 400
   Germantown, MD 20874
   USA

3. US SITES: Remind the parents as stated in the consent form, we will be reimbursing them $X for their time and trouble for each stool sample. A $X check will be issued by the clinic upon confirmation thatIf the Repository received the stool sample. Confirmation and issuing a check should be completed within one week.

4. Sites should stress the importance to the parents of keeping the vials and other items clean when the site introduces the stool collection process to the parent.

5. US sites should instruct the parent to be sure not to include the child's name, the parent's name or any other type of protected health information in the stool shipment that is sent to the Repository

6. Sites should remind parents that stool samples should only be sent to the Repository (for US sites) or the Clinical Center (for European sites) in the provided plastic tubes with caps. Stool samples should not be sent in plastic bags, diapers, etc.

7. Sites should instruct parents to contact study personnel at the local Clinical Center regarding questions related to stool sample collection (and any other TEDDY-related questions), not the NIDDK Repository.

8. If sites would like to review information on an individual subject's stool sample collection compliance, a link to an individualized stool sample

compliance report can be found at the top of each subject's Participant's Details Page.

15.6. Reminder Calls

Reminder calls to families one week prior to due date.

Stool Collection Reminder Call Script:

"Hi Mrs. (NAME),

This is (NAME) from the TEDDY STUDY, and I am calling to remind you that it's time to collect a stool sample from (CHILD'S NAME). This can be done anytime in the next week.

Do you have a mailer and collection kit?

[If yes,] Continue
[If no,] Send a new kit to the family and call in one week

Please collect and mail the sample during the week (Mon-Thurs), so it doesn't sit over the weekend.

Do you have any questions?

How are you doing with your TEDDY Book? Do you have any questions about the book or the study in general?

Thanks very much for your help. We will send your $X reimbursement after we get your child's sample. Have a good day!"

15.7. Shipping

15.7.1. US Clinical Centers

Monthly stool samples will be mailed from the US homes to the NIDDK Repository until the child is 48 months of age; after that parents will send stool samples from US homes to the NIDDK Repository every 3 months from 48 months of age until 10 years of age and every 6 months from 10 years of age through the end of the study. Shipping instructions for parents are listed in the "Instructions on how to collect poop sample (US Version)" located in the appendix of this section.

15.7.2. European Clinical Centers and US Clinical Centers Collecting Rectal Swab Samples

Monthly stool samples will be mailed from the European homes back to the European Clinical Centers until the child is 48 months of age; after

that parents will send stool samples from European homes to the European Clinical Centers every 3 months from 48 months of age until 10 years of age and every 6 months from 10 years of age through the end of the study. Shipping instructions for parents are listed in the "Instructions on how to collect poop sample" (European Version)" located in the appendix of this section.

Both European and US Clinical Centers may collect rectal swab samples from non-compliant subjects less than four years of age.

Bulk shipments of stool samples will be mailed from each of the European Clinical Centers and US Clinical Centers collecting rectal swab samples to the Repository once a month:

Entering information into the "Sample Shipment System"

Once a month each European clinical center and US Clinical Center collecting rectal swab samples will send bulk shipments of stool samples to the NIDDK Repository.

1. Logon to the TEDDY website, http://teddy.epi.usf.edu/.
2. Go to the "Sample Shipment System" located on the left navigational toolbar under "Data Management".
3. Enter the date of shipment.
4. If you have user access to more than one shipment origin, you will need to choose which destination the samples you are shipping are being shipped from. If you only have user access to one shipment origin, the 'Origin' drop-down menu will be defaulted to that location and you do not need to do anything
5. Choose the "Repository" destination option under "Select where samples will be shipped to".
6. Enter the box number for each freezer box that you are going to be shipping (in one package) separated by commas, and click "Search".
7. The Local Code, Subject ID, Clinical Center, Test Name, Vial Barcode Number, Visit Location Code, Date Draw, Box/Pouch Number, Space Number, Sample Volume, Site Number (this will only appear for samples being shipped to the Repository) and "Delete From Shipment" option will appear for all the samples that are located in each freezer box.
8. Enter the tracking number and courier service for that shipment and any comments you would like to notify the lab about.
9. Click on "Print and Email Shipping List". A dialog box will open that asks "Are you sure you want to print and email the shipment list?" Press 'OK' if you do and 'Cancel' if you don't.

10. Once 'OK' has been clicked an Excel file will be created that will contain information pertaining to each sample (Vial Barcode Number, Subject ID, etc).
11. Save this file for your records; an email containing this file will automatically be sent to the DCC and to the Repository.
12. Print out a copy of this list to be shipped with the samples. Make sure that this shipping list contains all of the samples that are being shipped with that particular shipment.
13. Repeat this process as necessary until all the boxes you will be sending that day have been entered.

Packing and Shipping Instructions for US Sites:

1. Please do not ship packages on Friday. The repository is closed for business on weekends.
2. Place the 3" freezer box along with a STP-152 absorbent strip inside a STP-731 inner leak proof poly (plastic) bag. Seal the bag.
3. Place the poly bag inside a STP-730 envelope, fold over and tuck the STP-730 into pocket.
4. Place up to three filled STP-730 envelopes in the cardboard inner box, tape the box shut and place it in the middle of the cooler in the STP-309 shipper. If there are only one or two vial boxes in the shipment, fill the rest of the space inside the cardboard inner box with packing material (e.g. bubble wrap or newspaper) to prevent movement during shipment.
5. Fill the remainder of the space between the cardboard box and the inner walls of the cooler with dry ice.
6. Put the lid on the cooler and place the excel printout (containing the sample information) on top of the cooler. Place the "empty packaging cover" (if included – this will be one piece of cardboard that is attached to the outside of the box) on top of the list.
7. Close and tape the outer cardboard box.
8. Place a checkmark in the block on the outer cardboard box next to "BIOLOGICAL SUBSTANCE, CATEGORY B". Do not cover this marking with labels.
9. Affix a label with your name and return address to the side of the box in the "Shipper" block.
10. Affix the repository address label to the side of the box in the "Consignee" block that reads:

Chris Deigan
Disease Prevention
Fisher BioServices
20301 Century Blvd.
Building 6, Suite 400
Germantown MD 20874

11. Affix the dry ice label below the repository address label. Enter the weight of dry ice on the label in kilograms.
12. Affix the "UN3373 BIOLOGICAL SUBSTANCE, CATEGORY B" label to the right of the dry ice label.
13. Use the pre-printed FedEx US air bill to ship the samples to the NIDDK Biosample Repository at Fisher Bioservices.
    a. In Section 1, enter the date, your name, return address and phone number. Leave "Sender's FedEx Account Number" blank
    b. Complete Section 6, Special Handling:
        i. Under "Does this shipment contain dangerous goods?" check "Yes, Shippers Declaration not required".
        ii. Check the "Dry Ice" block and enter "1" and the weight of dry ice in kg.
    c. Under Section 7, Payment:
        i. Enter "1" under "Total Packages".
        ii. Enter the total weight of the package under "Total Weight".
    d. Follow the peel and stick instructions on the back of the air bill (no document holder required).
    e. Attach the air bill to the side of the box adjacent to the labeled sie.
14. Call FedEx at 1.800.Go.FedEx® (800.463.3339) **or** go to http://www.fedex.com/us/ to schedule a pick-up
15. Notify the repository of the incoming shipment and tracking number via email (BIO-NIDDKRepository@FisherSci.com) or fax (301-515-4049) on the day the package is picked up by FedEx.

Packing and Shipping Instructions for European Sites:

1. Please plan for the arrival dates of your shipments -.the repository is closed for business on weekends.
2. Place the 3" freezer box along with an absorbent strip inside the inner leak proof poly (plastic) bag. Seal the bag.
3. Place the plastic bag inside the large Tyvek envelope, remove the strip of paper covering the adhesive on the flap, and seal the envelope closed.
4. Put a layer of dry ice in the bottom of the box. Place up to 5 Tyvek envelopes containing boxes on the dry ice.
5. Fill the remainder of the space in the shipper with dry ice up to about four inches from the top.
6. Put the foam insert on top of the dry ice in the opening. Place a copy of the manifest shipping form inside a zip-lock bag, and set it on top of the foam insert under the lid flaps.
7. Close and tape the cardboard box.
8. Attach all labels to the same side of the box:

a. Stick the dry ice label on the side of the box in the upper right corner. Enter the weight of dry ice as 14 kg.
b. Place the "UN3373 Diagnostic Specimens" label on the top, center, to the left of the dry ice label.
c. Stick the small address label below the "Up" arrows that reads:

Chris Deigan
Disease Prevention
Fisher BioServices
20301 Century Blvd.
Building 6, Suite 400
Germantown MD 20874

d. Place the CDC Import Permit label below the small address label. Enter the permit number (2010-03-171) and expiration date (13 May 2011).

9. Use the preprinted World House Air Way Bill (HAWB) to ship the samples to the Fisher/NIDDK Biosample Repository.
   a. Complete the sections of the HAWB that have not been pre-printed.
   b. Affix the HAWB to the exterior of the shipper. This form is an internal tracking form used by World to identify your shipment from pick-up to delivery. When inquiring about your shipment, reference the waybill number in the top right hand corner. World Courier will provide these forms to you with shipper and consignee information pre-printed.
   c. World will send you an example Customs Invoice, you need to copy this invoice to your letterhead, fill in information for the Date, Shipper, Consignee, and estimate the amount of sample contained in the shipment (in mL) and sign.
   d. Affix the Customs Invoice to the shipper exterior
   e. Along with the documents listed above, also give the signed Declaration Statement to the World Courier person picking up the shipment.
10. Call World Courier Services to arrange for pick-up:
    - Finland: 9 8700 3300
    - Germany: 89 9698 9290
    - Sweden: 8 59441 480

You will need to provide the following information to the World Courier Representative:

- Repository Account Number: 10765
- Time of Pick-up
- Specification of types of samples being sent
- Number and type of boxes being shipped
- Special Instructions: Diagnostic shipment.

11. Notify the repository by email (BIO-NIDDKRepository@FisherSci.com) of an incoming shipment on the day the package is picked up by World. Provide the tracking number, so the repository may track the shipment if it is delayed.

Section 15 Appendix

A. **Parent Instructions on How to Collect Poop Samples (US Version, Ambient Shipping, Collection from diaper)**
B. **Parent Instructions on How to Collect Poop Samples (US Version in Spanish, Ambient Shipping, Collection from diaper)**
C. **Parent Instructions on How to Collect Poop Samples (US Version, Ambient Shipping, Collection from toilet)**
D. **Parent Instructions on How to Collect Poop Samples (US Version in Spanish, Ambient Shipping, Collection from toilet)**
E. **Parent Instructions on How to Collect Poop Samples (US Version, Refrigerated Shipping, Collection from diaper)**
F. **Parent Instructions on How to Collect Poop Samples (US Version in Spanish, Refrigerated Shipping, Collection from diaper)**
G. **Parent Instructions on How to Collect Poop Samples (US Version, Refrigerated Shipping, Collection from toilet)**
H. **Parent Instructions on How to Collect Poop Samples (US Version in Spanish, Refrigerated Shipping, Collection from toilet)**
I. **Instructions on How to Collect Poop Samples (European Version)**
J. **German Instructions on How to Collect Poop Samples – Collection from diaper**
K. **German Instructions on How to Collect Poop Samples – Collection from toilet**
L. **Swedish Instructions on How to Collect Poop Samples – Collection from diaper (Sweden does not use instructions for collection from toilet)**
M. **Finnish Instructions on How to Collect Poop Samples – Collection from diaper**
N. **Finnish Instructions on How to Collect Poop Samples – Collection from toilet**

A. PARENT INSTRUCTIONS ON HOW TO COLLECT POOP SAMPLES (US VERSION, AMBIENT SHIPPING, COLLECTION FROM DIAPER)

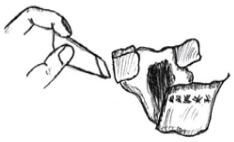
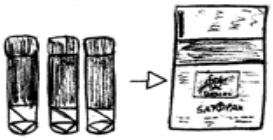
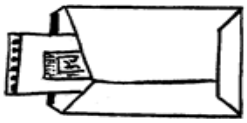
TEDDY
The Environmental Determinants of Diabetes in the Young

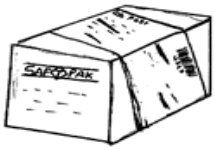
Date of Collection: ____/_____/_____
DD / MMM / YYYY

Instructions on how to collect poop sample

***** Please collect and mail the sample during the week (Mon-Thurs), so it doesn't sit over the weekend.**

Subject ID: **Local Code:**

	**1.** Remove dirty diaper. **2.** Unscrew the lid from one of the plastic containers. You will notice there is a small tube inside of the container. You will fill this small tube with the poop sample. **3.** Insert the tube into the poop. Using a scooping action, fill the inside of the collection tube until it is completely full. You may collect the poop sample over a 24 hour period, however if there is not enough poop sample to completely fill all three tubes, try to fill each tube halfway, rather than leaving some tubes empty. *(See Appendix 1 of your TEDDY Book if the poop is soaked into the diaper and cannot be collected by scooping.)
	**4.** Carefully place the filled collection tube back into the plastic container and screw the lid on tightly. **5.** Repeat steps 2-4 with the other 2 tubes. **6. Please wipe the outside of the tubes so that they are clean and please be sure not to get any poop sample on any of the items you will be sending.** **7.** Write the date of collection at the top of this sheet (in the space provided.)
	**8.** Put the 3 plastic containers, that have been filled with poop, in the clear plastic bag with the absorbent strip. Seal the bag by following the instructions on the bag.
	**9.** Place the plastic bag inside of the white envelope, remove the cover over the adhesive, and seal the envelope. **10.** Place this white paper envelope into the cardboard box. **11.** Fold this sheet and place it in the box with the white envelope and close the lid.
	**12.** Use the enclosed mailing label to send the package: • Fold the mailing label in half so that most of the "TO" address is on one side, and most of the "FROM" address is on the other. • Remove the backing to expose the adhesive. • Attach the mailing label over the TOP FRONT CORNER of the box as shown. The mailing label will seal the lid closed. Leave the right side of the label, nearest the end, unattached to the box (because the Post Office needs to remove copies from inside of the form).

	**13.** Give the box to the US Post Office in any of the following ways: • Put in your mailbox for postal carrier pickup. • Drop off at any US Post Office • Place in a US Post Office Express Mail drop box.

Form Revision Date: 15 May 2009

**** If the poop is soaked into the diaper choose 1 of the following options (instructions in TEDDY Book):***

1. Use scissors:
    a. Cut off a small section of your baby's diaper where some of the poop is soaked.
    b. Put this small section into the plastic poop container and screw the lid on tightly.
    c. Repeat steps 'a' and 'b' with the other 2 tubes
    d. Continue with steps 6-14 from above
2. Use a Q-tip:
    a. Rub the Q-tip against the wet diaper to soak and/or scrape some of the poop onto 1 of the cotton ends.
    b. Put the Q-tip into the plastic poop container (cutting off the opposite end, if necessary to make it fit) and screw the lid on tightly.
    c. Repeat steps 'a' and 'b' with the other 2 tubes
    d. Continue with steps 6-14 from above

B. PARENT INSTRUCTIONS ON HOW TO COLLECT POOP SAMPLES (US VERSION IN SPANISH, AMBIENT SHIPPING, COLLECTION FROM DIAPER)

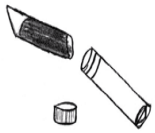
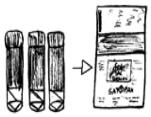
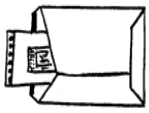
TEDDY
The Environmental Determinants of Diabetes in the Young

Fecha de Colección:___/_____/____ (**DD/MMM/AAAA)**

Instrucciones de como coleccionar muestra de excremento

*****Por favor coleccione y envié la muestra entre semana (lunjue), para que no se quede el fin de semana en la oficina postal.**

Participante ID: **Código local**

	**1.** Remueva el pañal sucio. **2.** Quite la tapadera de uno de los 3 contenedores plásticos. Notara que hay un pequeño tubo dentro del contenedor. R este pequeño tubo con la muestra de excremento. **3.** Inserte el tubo en el excremento. Usándolo como cuchara, llene el tubo de colección hasta que este completamente Usted puede coleccionar la muestra de excremento dentro de un periodo de 24 horas, sin embargo si no hay suficiente excremento para llenar completamente los tres tubos, intente llenarlos solo hasta la mitad, en vez de dejar algunos tu vacíos.
	**4.** Cuidadosamente ponga el tubo de colección lleno dentro del contenedor plástico y cierra la tapa. **5.** Repita los pasos 4-6 con los otros dos tubos. **6.** Por favor limpie el exterior de los contenedores completamente y por favor asegúrese de que no haya excremento e de los artículos que va a enviar. **7.** Escriba la fecha de colección en la parte de arriba de esta hoja (en el lugar previsto)
	**8.** Coloque los 3 contenedores plásticos que han sido llenados con excremento en la bolsa plástica con la tira blanca al Selle la bolsa siguiendo las instrucciones en la bolsa.
	**9.** Coloque la bolsa plástica dentro del sobre blanco de papel, remueva la cubierta que esta sobre el adhesivo y selle e **10.** Coloque el sobre de papel blanco dentro de la caja de cartón. **11.** Doble esta pagina y póngala encima de la tapa de la caja y cierre las pestañas. **12.** Use la etiqueta de envió incluida para enviar el paquete: • Remueva la parte trasera para exponer el adhesivo. • Pegue la etiqueta de envió encima de la caja. **13.** Lleve la caja a la oficina Postal de cualquiera de las siguientes maneras: • Coloque la caja en su buzón para que el cartero la recoja. • Llévela a cualquier Oficina Postal US. • Colóquela en cualquier Buzón Express de US Post Office Express Mail .

Form Revision Date: 15 May 2009

C. PARENT INSTRUCTIONS ON HOW TO COLLECT POOP SAMPLES (US VERSION, AMBIENT SHIPPING, COLLECTION FROM TOILET)

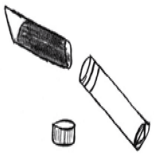
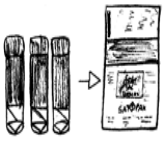
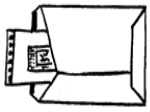
TEDDY
The Environmental Determinants of Diabetes in the Young

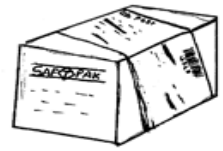
Date of Collection:____/_____/_____ (DD/MMM/YYYY)

Instructions on how to collect poop sample (with collection device)

***** Please collect and mail the sample during the week (Mon-Thurs), so it doesn't sit over the weekend.**

Subject ID: **Local Code:**

	**1.** Place provided stool collection device under toilet seat in center of rear of toilet bowl and cl to hold the device in place. **2.** After child has pooped inside of the collection device, remove device from toilet (it is okay i pee mixed with the poop inside of the collection device). **3.** Unscrew the lid from one of the three plastic containers. You will notice there is a small tub container. You will fill this small tube with the poop sample. **4**. Insert the tube into the poop. Using a scooping action, fill the inside of the collection tube u completely full. You may collect the poop sample over a 24 hour period, however if there is no sample to completely fill all three tubes, try to fill each tube halfway, rather than leaving some **5**. Carefully place the filled collection tube back into the plastic container and screw the lid on **6**. Repeat steps 3-5 with the other two tubes. **7**. Flush any remaining poop and pee left in the collection device down your toilet; place the p the collection device and place it in the garbage. **8. Please wipe the outside of the tubes so that they are clean and please be sure not poop sample on any of the items you will be sending.** **9**. Write the date of collection at the top of this sheet (in the space provided).
	**10**. Put the 3 plastic containers that have been filled with poop in the clear plastic bag with th absorbent strip. Seal the bag by following the instructions on the bag.
	**11**. Place the plastic bag inside of the white paper envelope, remove the cover over the adhes the envelope. **12**. Place this white paper envelope into the cardboard box. **13**. Fold this sheet and place it in the box with the white envelope and close the lid.



14. Use the enclosed mailing label to send the package:

- Fold the mailing label in half so that most of the "TO" address is on one side, and mos "FROM" address is on the other.
- Remove the backing to expose the adhesive.
- Attach the mailing label over the TOP FRONT CORNER of the box as shown. The mailin seal the lid closed. Leave the right side of the label, nearest the end, unattached to th (because the Post Office needs to remove copies from inside of the form).

15. Give the box to the US Post Office in any of the following ways:

- Put in your mailbox for postal carrier pickup.
- Drop off at any US Post Office.
- Place in a US Post Office Express Mail drop box.

Form Revision Date: 15 May 2009

D. PARENT INSTRUCTIONS ON HOW TO COLLECT POOP SAMPLES (US VERSION IN SPANISH, AMBIENT SHIPPING, COLLECTION FROM TOILET)

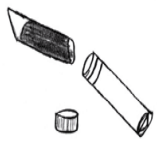
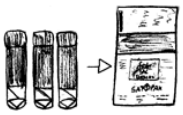
TEDDY
The Environmental Determinants of Diabetes in the Young
Fecha de Colección:___/_____/____ (**DD/MMM/AAAA)**

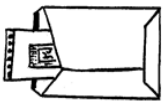
Instrucciones para la toma de la muestra de excremento (popó)

(aparato para recolectar y enviar en época de invierno)

***** Por favor tome la muestra y envíela durante los días de la semana (de lunes a jue**
para que la muestra no se quede sin enviar durante el fin de semana

Participante ID: **Código local**

	1. Coloque el aparato para recolectar la muestra de excremento/popó debajo del asiento del inodoro en el ce posterior del inodoro y baje el asiento para que éste asegure el aparato en su sitio. 2. Después de que el niño haya dejado el excremento/hecho popó dentro del aparato para recopilar la muest aparato del inodoro (no hay problema si también hay orina mezclada con popó dentro del aparato para recol muestra). 3. Quítele la tapa a uno de los tres contenedores plásticos. Usted podrá observar que hay un tubo pequeño c contenedor. Usted debe llenar dicho tubo con la muestra de excremento/popó. 4. Inserte el tubo en la popó. Como si se tratara de un movimiento de recoger con una pala o cuchara, llene tubo de recolección hasta llenarlo completamente. Puede recolectar la muestra de excremento durante un p horas. Sin embargo si no hay suficiente excremento para llenar completamente los tres contenedores, trate tubo hasta la mitad, en lugar de dejar algún tubo desocupado. 5. Con cuidado coloque de nuevo el tubo de recolección ya lleno dentro del contenedor de plástico y ciérrelo Apriete la tapa totalmente. 6. Repita exactamente los pasos del 3 al 5 para los otros dos tubos. 7. Cualquier excremento u orina sobrante puede echarlas al inodoro; coloque la tapa que le proporcionamos aparato para la recolección de la muestra y bótelo a la basura. 8. Por favor limpie el exterior de los contenedores completamente y asegúrese de que no haya excremento en ninguno de los artículos q enviar. 9. Escriba la fecha de la recolección en la parte superior de esta página (en el espacio provisto).
	10. Coloque los tres contenedores plásticos llenos de excremento en la bolsa de plástico transparente con la blanca. Selle la bolsa. Siga las instrucciones que aparecen en la bolsa.



11. Coloque la bolsa de plástico dentro del sobre de papel blanco, quítele el adhesivo y selle el sobre.

12. Coloque este sobre de papel blanco en la caja de cartón.

13. Doble esta hoja y colóquela dentro de la caja junto con el sobre blanco; cierre la caja.

14. Use la etiqueta adjunta para enviar el paquete.

• Doble la etiqueta por la mitad para que la mayor parte de la dirección "TO"(PARA) quede a un lado, y la ma
dirección "FROM" (DE) quede al otro lado.

• Retire el papel que está detrás de la etiqueta para que el adhesivo quede expuesto.

• Coloque la etiqueta sobre la ESQUINA DE ARRIBA DEL FRENTE DE LA CAJA según se indica en la figura. La
envío postal sellará la tapa de la caja para que quede cerrada. Deje el lado derecho de la etiqueta, el más ce
pegarse a la caja. (Esto se hace porque la Oficina Postal necesita sacar las copias del interior del formulario)

15. Por favor tome la muestra y envíela durante los días de la semana (de lunes a jueves), para que la mues
sin enviar durante el fin de semana

16. Entregue la caja a la Oficina Postal de cualquiera de las siguientes maneras:

• Colóquela en su buzón personal para que el cartero la recoja.

• Déjela en cualquier Oficina Postal.

• Colóquela en un buzón para Correo Express de la Oficina Postal de los Estados Unidos.

Form Revision Date: 15 May 2009

E. PARENT INSTRUCTIONS ON HOW TO COLLECT POOP SAMPLES (US VERSION, REFRIGERATED SHIPPING, COLLECTION FROM DIAPER)

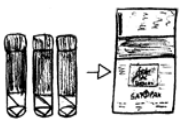
TEDDY
The Environmental Determinants of Diabetes in the Young

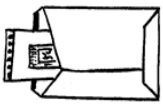
Date of Collection:____/_____/_____
DD / MMM / YYYY

Instructions on how to collect poop sample

***** Please collect and mail the sample during the week (Mon-Thurs), so it doesn't sit over the weekend.**

Subject ID: **Local Code:**

	1. Place box in freezer (do not remove any of its contents). Please make sure this box has been in the freezer for a hours before using, the gel packs should be frozen solid. **2**. Pull out the envelope from the center of the gel packs, place box back in freezer. This envelope contains the tub use for collecting the sample. Once you are finished getting the sample, the tubes will go back into the bag and en envelope should then be placed in the middle of the gel packs just as it was when you started.
 	**3.** Remove dirty diaper. **4.** Unscrew the lid from one of the plastic containers. You will notice there is a small tube inside of the container. Y this small tube with the poop sample. **5.** Insert the tube into the poop. Using a scooping action, fill the inside of the collection tube until it is completely may collect the poop sample over a 24 hour period, however if there is not enough poop sample to completely fill a tubes, try to fill each tube halfway, rather than leaving some tubes empty. *(See Appendix 1 of your TEDDY Book soaked into the diaper and cannot be collected by scooping.) **6.** Carefully place the filled collection tube back into the plastic container and screw the lid on tightly. **7.** Repeat steps 4-6 with the other 2 tubes. **8. Please wipe the outside of the tubes so that they are clean and please be sure not to get any poop sa any of the items you will be sending.** **9.** Write the date of collection at the top of this sheet (in the space provided.)
	**10**. Put the 3 plastic containers that have been filled with poop in the clear plastic bag with the white absorbent str bag by following the instructions on the bag.
	11. Place the plastic bag inside of the white paper envelope, remove the cover over the adhesive, and seal the env **12**. Take box from freezer right before you intend to mail samples (make sure gel packs are frozen). **13**. Place white paper envelope inside of Styrofoam box in between gel packs and put lid on Styrofoam container. **14**. Fold this sheet and place it on top of the Styrofoam lid; close the flaps. **15**. Wet the gummed tape with a damp sponge or paper towel. Place the tape the long way over the top of the box



two flaps shut.
16. Use the enclosed mailing label to send the package:

- Remove the backing to expose the adhesive.
- Attach the mailing label on the TOP of the box.

17. Give the box to the US Post Office in any of the following ways:

- Put in your mailbox for postal carrier pickup.
- Drop off at any US Post Office.
- Place in a US Post Office Express Mail drop box.

Form Revision Date: 15 May 2009

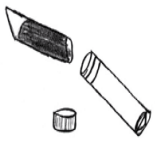
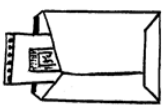
F. PARENT INSTRUCTIONS ON HOW TO COLLECT POOP SAMPLES (US VERSION IN SPANISH, REFRIGERATED SHIPPING, COLLECTION FROM DIAPER)

TEDDY
The Environmental Determinants of Diabetes in the Young
Fecha de Colección:___/_____/____ (**DD/MMM/AAAA)**

Instrucciones de como coleccionar muestra de excremento

*****Por favor coleccione y envié la muestra entre semana (lunjue), para que no se quede el fin de semana en la oficina postal.**

Participante ID: **Código local**

	1. Coloque la caja en el congelador (no remueva nada del contenido). Por favor asegúrese que la caja ha est menos 12 horas ahí antes de usarse, los paquetes de gel deben estar congelados solidamente. **2.** Saque el sobre del centro de los paquetes de gel. Ponga la caja en el congelador. Este sobre contiene los t para coleccionar la muestra. Una vez que termine de obtener la muestra los tubos irán dentro de la bolsa y e sobre va en medio de los paquetes de gel como estaba cuando empezó.
 	**3.** Remueva el pañal sucio. **4.** Quite la tapadera de uno de los 3 contenedores plásticos. Notara que hay un pequeño tubo dentro del con Llenara este pequeño tubo con la muestra de excremento. **5.** Inserte el tubo en el excremento. Usándolo como cuchara, llene el tubo de colección hasta que este compl Usted puede coleccionar la muestra de excremento dentro de un periodo de 24 horas, sin embargo si no hay excremento para llenar completamente los tres tubos, intente llenarlos solo hasta la mitad, en vez de dejar a vacíos. **6.** Cuidadosamente ponga el tubo de colección lleno dentro del contenedor plástico y cierra la tapa. **7**. Repita los pasos 4-6 con los otros dos tubos. **8**. Por favor limpie el exterior de los contenedores completamente y por favor asegúrese de que no haya exc ninguno de los artículos que va a enviar. **9**. Escriba la fecha de colección en la parte de arriba de esta hoja (en el lugar previsto)
	**10.** Coloque los 3 contenedores plásticos que han sido llenados con excremento en la bolsa plástica con la ti absorbente. Selle la bolsa siguiendo las instrucciones en la bolsa.
	**11.** Coloque la bolsa plástica dentro del sobre blanco de papel, remueva la cubierta que esta sobre el adhesi sobre. **12.** Tome la caja del congelador poco antes de que intente enviar las muestras (asegúrese que los paquetes congelados). **13.** Coloque el sobre de papel blanco dentro de la caja de Nieve seca en medio de los paquetes de gel y colo contenedor de Nieve seca. **14.** Doble esta pagina y póngala encima de la tapa de la caja de nieve seca; cierre las pestañas. **15.** Moje la tira con pegamento con una esponja húmeda o una toalla de papel. Coloque la tira a lo largo y s para cerrar las dos pestañas. **16.** Use la etiqueta de envió incluida para enviar el paquete: • Remueva la parte trasera para exponer el adhesivo. • Pegue la etiqueta de envió encima de la caja. **17.** Lleve la caja a la oficina Postal de cualquiera de las siguientes maneras: • Coloque la caja en su buzón para que el cartero la recoja. • Llévela a cualquier Oficina Postal US.

	• Colóquela en cualquier Buzón Express de US Post Office Express Mail .

Form Revision Date: 15 May 2009

G. PARENT INSTRUCTIONS ON HOW TO COLLECT POOP SAMPLES (US VERSION, REFRIGERATED SHIPPING, COLLECTION FROM TOILET)

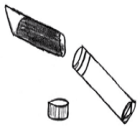
TEDDY
The Environmental Determinants of Diabetes in the Young

Date of Collection:___/_____/____ (DD/MMM/YYYY)

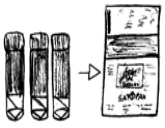
Instructions on how to collect poop sample (with collection device)

***** Please collect and mail the sample during the week (Mon-Thurs), so it doesn't sit over the weekend.**

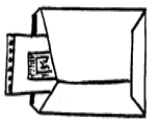
Subject ID: **Local Code:**



1. Place box in freezer (do not remove any of its contents). Please make sure this box has been in the freez
12 hours before using, the gel packs should be frozen solid.
2. Pull out the envelope from the center of the gel packs, place box back in freezer. This envelope contains
will use for collecting the sample. Once you are finished getting the sample, the tubes will go back into the
envelope. The envelope should then be placed in the middle of the gel packs just as it was when you started
3. Place provided stool collection device under toilet seat in center of rear of toilet bowl and close toilet seat
device in place.
4. After child has pooped inside of the collection device, remove device from toilet (it is okay if there is also
the poop inside of the collection device).
5. Unscrew the lid from one of the three plastic containers. You will notice there is a small tube inside of the
will fill this small tube with the poop sample.
6. Insert the tube into the poop. Using a scooping action, fill the inside of the collection tube until it is comp
may collect the poop sample over a 24 hour period, however if there is not enough poop sample to complet
tubes, try to fill each tube halfway, rather than leaving some tubes empty.
7. Carefully place the filled collection tube back into the plastic container and screw the lid on tightly.
8. Repeat steps 5-7 with the other two tubes.
9. Flush any remaining poop and pee left in the collection device down your toilet; place the provided lid on
device and place it in the garbage.
10. Please wipe the outside of the tubes so that they are clean and please be sure not to get any on any of the items you will be sending.
11. Write the date of collection at the top of this sheet (in the space provided).



12. Put the 3 plastic containers that have been filled with poop in the clear plastic bag with the white absorb
the bag by following the instructions on the bag.



13. Place the plastic bag inside of the white paper envelope, remove the cover over the adhesive, and seal
14. Take box from freezer right before you intend to mail samples (make sure gel packs are frozen).
15. Place white paper envelope inside of Styrofoam box in between gel packs and put lid on Styrofoam cont
16. Fold this sheet and place it on top of the Styrofoam lid; close the flaps.
17. Wet the gummed tape with a damp sponge or paper towel. Place the tape the long way over the top of the two flaps shut.
18. Use the enclosed mailing label to send the package:

- Remove the backing to expose the adhesive.
- Attach the mailing label on the TOP of the box.

19. Give the box to the US Post Office in any of the following ways:

- Put in your mailbox for postal carrier pickup.
- Drop off at any US Post Office.
- Place in a US Post Office Express Mail drop box.

Form Revision Date: 15 May 2009

H. PARENT INSTRUCTIONS ON HOW TO COLLECT POOP SAMPLES (US VERSION IN SPANISH, REFRIGERATED SHIPPING, COLLECTION FROM TOILET)

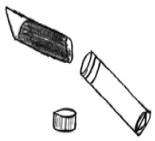
TEDDY
The Environmental Determinants of Diabetes in the Young
Fecha de Colección:___/_____/_____ (**DD/MMM/AAAA)**

Instrucciones para la toma de la muestra de excremento/popó

(aparato para recolectar y enviar la muestra en época de verano)

***** Por favor tome la muestra y envíela durante los días de la semana (de lunes a jue**
para que la muestra no se quede sin enviar durante el fin de semana

Participante ID: **Código local**



1. Coloque la caja en el congelador de su refrigerador (No remueva de sus contenidos). Por favor cerciórese de que la caja haya estado congelador al menos 12 horas. Antes de usar, los paquetes de gel d estar totalmente congelados.

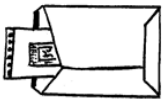
2. Saque el sobre que está en el centro de los paquetes de gel cong Vuelva a colocar la caja en el congelador. Este sobre contiene los tu usted habrá de utilizar para recolectar la muestra. Una vez que uste terminado de recolectar la muestra, los tubos tendrán que regresars bolsa y al sobre. El sobre debe colocarse en el medio de los paquete congelados de la misma manera que estaba cuando usted comenzó proceso.

3. Coloque el aparato para recolectar la muestra de excremento/pop del asiento del inodoro en el centro de la parte posterior del inodoro asiento para que éste asegure el aparato en su sitio.

4. Después de que el niño haya dejado el excremento/hecho popó d aparato para recopilar la muestra, retire el aparato del inodoro (no h problema si también hay orina mezclada con el popó dentro del apa recolectar la muestra).

5. Quítele la tapa a uno de los tres contenedores plásticos. Usted po observar que hay un tubo pequeño dentro del contenedor. Usted de dicho tubo con la muestra de excremento/popó.

6. Inserte el tubo en la popó. Como si se tratara de un movimiento

	recoger con una pala o cuchara, llene el interior del tubo de recolecc llenarlo completamente. Puede recolectar la muestra de excremento un perdió de 24 horas. Sin embargo si no hay suficiente excremento llenar completamente los tres contenedores, trate de llenar cada tub la mitad, en lugar de dejar algún tubo desocupado. 7. Con cuidado coloque de nuevo el tubo de recolección ya lleno den contenedor de plástico y ciérrelo muy bien. Ajuste la tapa totalment 8. Repita exactamente los pasos del 5 al 7 para los otros dos tubos. 9. Cualquier excremento u orina sobrante puede echarlas al inodoro la tapa que le proporcionamos sobre el aparato para la recolección d muestra y bótelo a la basura. 10. Por favor limpie el exterior de los contenedores completamente favor asegúrese de que no haya excremento en ninguno de los artíc va a enviar. 11. Escriba la fecha de la recolección en la parte superior de esta página (en el espacio provisto).
	12. Coloque los tres contenedores plásticos llenos de excremento en la bolsa de plástico transparente con la blanca. Selle la bolsa. Siga las instrucciones que aparecen en la bolsa.
	13. Coloque la bolsa de plástico dentro del sobre de papel blanco, quítele el adhesivo y selle el sobre. 14. Saque la caja del congelador sólo en el momento que vaya a en correo. (Asegúrese de que los paquetes de gel estén congelados). 15. Coloque el sobre de papel blanco dentro de la caja de espuma d poliestireno (styrofoam) en medio de los paquetes de gel congelado coloque la tapa en el contenedor de espuma de poliestireno. 16. Doble esta hoja y colóquela encima de la tapa de la caja de espu poliestireno (styrofoam); cierre los lados. 17. Humedezca la cinta con una toalla o esponja mojada. Coloque la lo largo de la parte superior de la caja para sellar los lados. 18. Use la etiqueta adjunta para enviar el paquete. • Retire el papel que está detrás de la etiqueta para qu

	adhesivo quede expuesto. • Pegue la etiqueta a la parte SUPERIOR de la caja. 19. Entregue la caja a la Oficina Postal de cualquiera de las siguient maneras: • Colóquela en su buzón personal para que el cartero l • Déjela en cualquier Oficina Postal. • C lóquela en un buzón para Correo Express de la Oficina Postal de los Estados Unido

Form Revision Date: 15 May 2009

I. INSTRUCTIONS ON HOW TO COLLECT POOP SAMPLES (EUROPEAN VERSION)

*** Please collect and mail the sample during the week (Mon-Thurs), so it doesn't sit over the weekend.

1. Remove the dirty diaper and put on the gloves provided.
2. Unscrew the lid from one of the plastic containers. You will notice there is a small tube inside of the container. You will fill this small tube half full with the poop sample.
3. Insert the tube into the poop. Using a scooping action, fill the inside of the collection tube until it is half full. *(See below if the poop is soaked into the diaper and cannot be collected by scooping)
4. Carefully place the filled collection tube back into the plastic container and screw the lid on tightly.
5. Repeat steps 2-4 with the other 2 tubes.
6. Write the date of collection at the top of this sheet (in the space provided).
7. Put the 3 plastic containers, that have been filled with poop, in the clear plastic bag with the white absorbent strip. Seal the bag by following the instructions on the bag.
8. Place the plastic bag inside of the white paper envelope, remove the cover over the adhesive, and seal the envelope.
9. Place the white paper envelope (containing the clear plastic bag with 3 stool containers) into the cardboard box.
10. Fold this sheet and place it into the box with the white envelope and close the lid.
11. **SITE-SPECIFIC SHIPPING INSTRUCTIONS (see Appendices F, G and H)**
12. Collect and mail the sample Mon – Thurs, so that the sample will not sit too long before freezer storage.

** If the poop is soaked into the diaper choose 1 of the following options (instructions in TEDDY Book):*

1. Use scissors:
    a. Cut off a small section of your baby's diaper where some of the poop is soaked.
    b. Put this small section into the plastic poop container and screw the lid on tightly.
    c. Repeat steps 'a' and 'b' with the other 2 tubes
    d. Continue with steps 6-14 from above
2. Use a Q-tip:
    a. Rub the Q-tip against the wet diaper to soak and/or scrape some of the poop onto 1 of the cotton ends.
    b. Put the Q-tip into the plastic poop container (cutting off the opposite end, if necessary to make it fit) and screw the lid on tightly.
    c. Repeat steps 'a' and 'b' with the other 2 tubes
    d. Continue with steps 6-14 from above

J. GERMAN INSTRUCTIONS ON HOW TO COLLECT POOP SAMPLES – COLLECTION FROM DIAPER

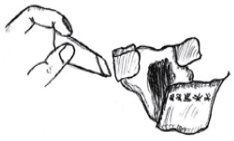
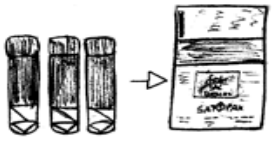
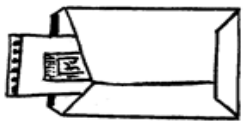
TEDDY
The Environmental Determinants of Diabetes in the Young

Datum der Stuhlprobe: ___/_____/____ (TT/ MMM /JJJJ) **Uhrzeit: __ __ : __ __**

ANLEITUNG FÜR DAS SAMMELN DER STUHLPROBEN

Bitte sammeln und verschicken Sie die Stuhlproben unter der Woche (Montag-Donnerstag), so dass die Probe über das Wochenende nicht unbearbeitet bleibt.

Subject ID: **Local Code:**

	**1** . Entfernen Sie die verschmutzte Windel und ziehen Sie sich die Handschuhe an. **2.** Schrauben Sie den Deckel eines der Plastikbehälter ab. Sie sehen innerhalb des Behälters ein klei Röhrchen. Dieses kleine Röhrchen wird mit der Stuhlprobe gefüllt. **3**. Führen Sie das Röhrchen in den Stuhl. Füllen Sie mit einer schaufelnden Bewegung das Röhrchen halbwegs voll ist.
	**4**. Stecken Sie vorsichtig das gefüllte Sammelröhrchen in den Plastikbehälter und schrauben Sie den fest zu. **5**. Wiederholen Sie Schritt 2-4 mit den anderen beiden Röhrchen. Bitte stellen Sie sichern, dass die Plastikbehälter außen sauber sind. **6**. Den Plastikbehältern liegt ein Blatt bei. Schreiben Sie auf dieses Datum und Uhrzeit, an dem die S gesammelt wurde.
	**7.** Stecken Sie die 3 Plastikbehälter, die mit Stuhl gefüllt sind, in die durchsichtige Plastiktüte mit de saugfähigem Material. Verschließen Sie die Tüte nach der aufgedruckten Anleitung.
	**8.**Stecken Sie die Plastiktüte in den weißen Papierumschlag und kleben Sie diesen zu. **9.** Stecken Sie den weißen Papierumschlag (der die durchsichtige Plastiktüte mit den 3 Stuhlproben e den braunen Versandkarton. **10.** Schicken Sie den braunen Versandkarton gemäß der Versandanweisungen an das Institut für Diabetesforschung

Form Revision Date: 19 May 2009

K. GERMAN INSTRUCTIONS ON HOW TO COLLECT POOP SAMPLES – COLLECTION FROM TOILET

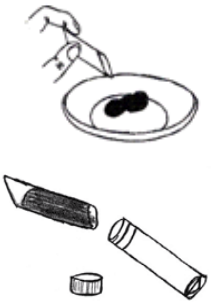
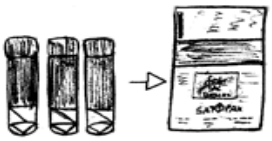
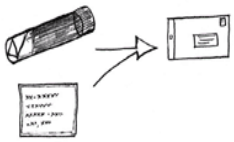
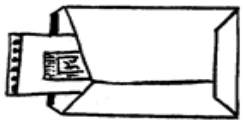
TEDDY
The Environmental Determinants of Diabetes in the Young

Datum der Stuhlprobe:___/_____/____
(TT/ MMM /JJJJ)

ANLEITUNG FÜR DAS SAMMELN DER STUHLPROBEN MIT DEM STUHLSAMMELBEHÄLTER

Bitte sammeln und verschicken Sie die Stuhlprobe unter der Woche (Montag-Donnerstag), so dass die Probe über das Wochenende nicht unbearbeitet bleibt.

Subject ID: **Local Code:**

	**1.** Stecken Sie den Stuhlsammelbehälter in die Halterung und platzieren Sie ihn zwischen Toilettensc und Toilettensitz. Klappen Sie den Toilettensitz herunter und lassen Sie ihr Kind zur Toilette gehen. E Ordnung, wenn Urin in den Stuhl gelangt. **2.** Nach dem Stuhlgang Ihres Kindes entfernen Sie den Behälter von der Toilette.
	**3.** Schrauben Sie den Deckel eines der Plastikbehälter ab und führen Sie das innen liegende Röhrche Stuhl. Füllen Sie mit einer schaufelnden Bewegung das Röhrchen bis es halbwegs voll ist. **4.** Stecken Sie das gefüllte Sammelröhrchen vorsichtig in den Plastikbehälter und schrauben Sie den fest zu
	**5.** Wiederholen Sie Schritt 3 und 4 mit den anderen beiden Röhrchen. Bitte stellen Sie sichern, dass die Plastikbehälter außen sauber sind. **6.** Den Plastikbehältern liegt ein Blatt bei. Schreiben Sie auf dieses Datum und Uhrzeit, an dem die S gesammelt wurde.
	**7.** Stecken Sie die 3 Plastikbehälter, die mit Stuhl gefüllt sind, sowie den mit Datum und Uhrzeit vers Zettel in die durchsichtige Plastiktüte. Verschließen Sie die Tüte nach der aufgedruckten Anleitung.
	**8.** Stecken Sie die Plastiktüte in den weißen Papierumschlag und kleben Sie diesen zu. **9.** Stecken Sie den weißen Papierumschlag (der die durchsichtige Plastiktüte mit den 3 Stuhlproben e den braunen Versandkarton. **10.** Schicken Sie den braunen Versandkarton gemäß der Versandanweisungen an das Institut für Diabetesforschung

Form Revision Date: 19 May 2009

L. SWEDISH INSTRUCTIONS ON HOW TO COLLECT POOP SAMPLES – COLLECTION FROM DIAPER

INSTRUKTION FÖR INSAMLING AV AVFÖRINGSPROV (BAJSPROV)

1. Ta av barnet blöjan.

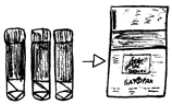
2. Skruva av locket från plastbehållaren. Inuti finns ett plaströr med skopa, som används för att fylla plastbehållaren med avföring.

3. Skopa upp avföring i plastskopan till dess den är fylld till hälften. (Om bajset är helt uppsuget i blöjan och inte kan skopas upp följ instruktionerna nedan*.)

4. Stoppa i det halvfyllda röret i plastbehållaren och skruva på locket ordentligt.

5. Gör samma sak (steg 2-4) med ytterligare 2 rör.

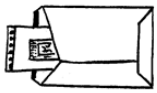
6. Skriv ned dagens datum på blanketten som ligger i förpackningen.



7. Stoppa de 3 plaströren som fyllts med avföring i plastpåsen. Ta inte bort det vita filterpappret från påsen.

8. Stäng igen plastpåsen.

9. Stoppa plastpåsen med prover i det bruna vadderade kuvertet.



10. Vik ihop blanketten och lägg också den i det bruna kuvertet.

11. Klistra igen kuvertet.

12. Posta kuvertet med proverna så snart som möjligt. Kontrollera att brevlådan kommer att tömmas under dagen så provet inte blir liggande i brevlådan över natten.

13. Samla och skicka avföringsproverna måndag-torsdag så proverna inte blir liggande för länge innan de kan tas om hand och frysas in i TEDDY-laboratoriet.

***) Om bajset är helt uppsuget i blöjan gör något av följande (A eller B):**

A - Klipp av en liten bit blöja med bajs och stoppa den i plastbehållaren. Skruva på locket.
- Gör likadant med ytterligare två blöjbitar. Följ sedan instruktionerna enligt ovan (6-13).

eller

B
- Gnid – skrubba – den våta blöjan med en bomullstops och sug upp eller skrapa upp lite bajs på ena änden av topsen.
- Stoppa topsen i plastbehållaren. (Klipp av den ”rena” delen om topsen är för lång.) Stäng locket.
- Gör samma sak med ytterligare 2 tops. Följ sedan instruktionerna enligt punkt 6-13.

M. FINNISH INSTRUCTIONS ON HOW TO COLLECT POOP SAMPLES – COLLECTION FROM DIAPER

KAKKANÄYTTEEN OTTO-OHJEET

Näyte otetaan ja lähetetään alkuviikosta (maantaina-torstaina), jotta se ei jää postiin viikonlopun ajaksi.

Pankaa koko näytepakkaus putkineen pakastimeen jäätymään vähintään 12 tuntia ennen näytteen ottamista.

Riisukaa lapselta kakkavaippa ja avatkaa paketissa oleva näyteputki. Sen sisällä on pienempi putki, johon kakkanäyte otetaan.

1. Työntäkää putki vaipassa olevaan kakkaan, täyttäkää putkesta noin 2/3 ja pankaa se isompaan näyteputkeen.
   Jos kakka on täysin imeytynyt vaippaan, leikatkaa vaipasta pieni pala ja pankaa se näyteputkeen. Voitte myös hieroa vanupuikon toista päätä kosteaan vaippaan, jolloin siihen imeytyy tai tarttuu kakkaa. Pankaa vanupuikko keräysputkeen, ja leikatkaa tarvittaessa toinen pää pois.
2. Täyttäkää kaikki pakkauksessa olevat näyteputket. On tärkeämpää saada pieni määrä näytettä useaan putkeen kuin isompi määrä yhteen putkeen. Vähimmäismäärä putkea kohti voi olla pikkulapsen kynnen kokoinen pala kakkaa.
3. Kiertäkää putkien korkit tiukasti kiinni.
4. Pankaa näyteputket minigrip-pussissa pahvilaatikkoon imuliinan ja kylmägeelin väliin. Lähettäkää myös mahdolliset tyhjät putket! Merkitkää pakkauksessa olevaan tarraan näytteenoton päivämäärä. Tarrat pannaan sellaisenaan pakettiin, niitä ei liimata putkiin. Kiertäkää kuminauha kaksi kertaa lähetyslaatikon ympäri, jotta laatikko pysyy kiinni kuljetuksen aikana. Lähetyslaatikossa on osoite valmiina. Postimaksu on etukäteen maksettu.
5. Pankaa lähetyspakkaus postilaatikkoon ennen postilaatikon tyhjentämistä, jolloin se lähtee samana päivänä eteenpäin, tai viekää se suoraan postitoimistoon.

KIITOKSIA VAIVANNÄÖSTÄ!

N. FINNISH INSTRUCTIONS ON HOW TO COLLECT POOP SAMPLES – COLLECTION FROM TOILET

TEDDY-tutkimus
Ohjeet kakkanäytteiden keräämisestä ja lähettämisestä

Lapseltanne tulisi ottaa kakkanäyte kerran kuukaudessa ja lähettää se postitse Tampereen yliopiston lääketieteen laitoksen virologian laboratorioon. Tätä varten Teille on annettu näytepakkaus, johon kuuluu keltamusta postituslaatikko (postimaksu maksettu), sen sisällä kylmägeeli ja muovipussissa olevat näytteenottoputket sekä pahvinen kertakäyttölautanen.

Näyte otetaan ja lähetetään alkuviikosta (maanantaina - torstaina), jotta se ei jää postiin viikonlopun ajaksi.

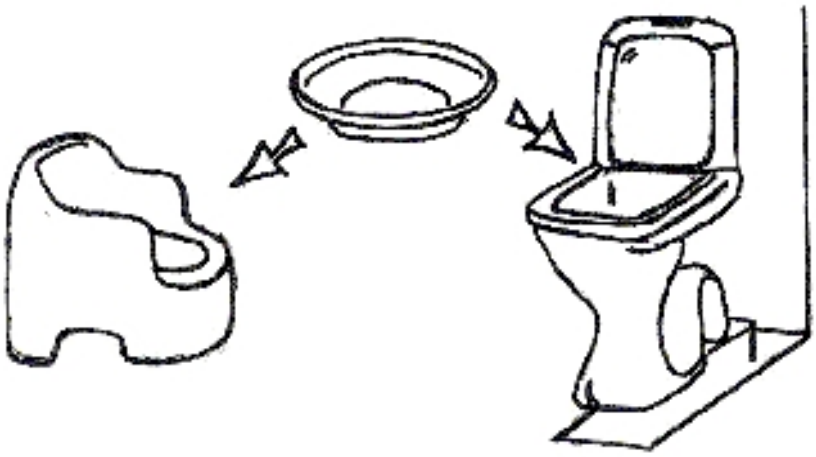
Pankaa koko näytepakkaus putkineen pakastimeen jäätymään vähintään 12 tuntia ennen näytteen ottamista, jolloin kylmägeeli jäätyy ja näyteputket painavat siihen kolon.

Näyte otetaan joko pottaan tai WC-istuimeen laitetun pahvisen kertakäyttölautasen päältä (ohessa).

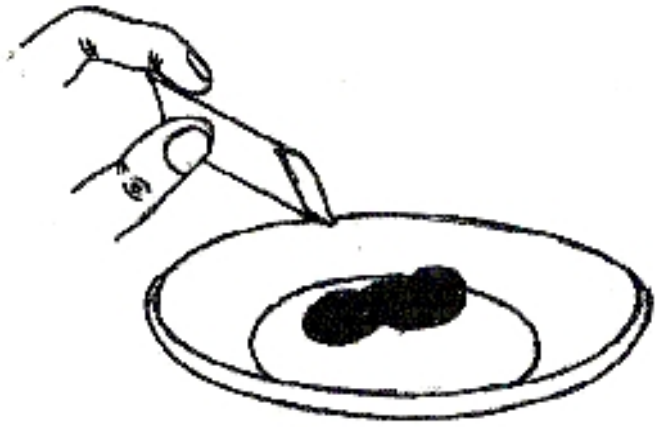
1. Ennen näytteenottoa näytepakkaus otetaan pakastimesta ja sen sisällä olevat näyteputket avataan.
2. Putkien sisällä oleva muovihylsy työnnetään kakkaan, jolloin hylsyn sisään pyritään ottamaan mahdollisimman paljon näytettä (ks. oheinen kuva). Tämän jälkeen hylsy pannaan takaisin näyteputken sisään.
3. Täyttäkää kaikki pakkauksessa olevat näyteputket. On tärkeämpää saada pieni määrä näytettä useaan putkeen kuin isompi määrä yhteen putkeen. Vähimmäismäärä putkea kohti voi olla pikkulapsen kynnen kokoinen pala kakkaa.
4. Kiertäkää putkien korkit tiukasti kiinni.
5. Pankaa näyteputket minigrip-pussissa pahvilaatikkoon imuliinan ja kylmägeelin väliin. Lähettäkää myös mahdolliset tyhjät putket! Merkitkää pakkauksessa olevaan tarraan näytteenoton päivämäärä. Tarrat pannaan sellaisenaan pakettiin, niitä ei liimata putkiin.
6. Lähetyslaatikossa on osoite valmiina, ja postimaksu on maksettu etukäteen. Laatikon pysymisen suljettuna kuljetuksen aikana voi varmistaa teipinpalalla.
7. Pankaa lähetyspakkaus postilaatikkoon ennen postilaatikon tyhjentämistä, jolloin se lähtee samana päivänä eteenpäin, tai viekää se suoraan postitoimistoon.

Kiitoksia vaivannäöstänne!

Kakkanäytteen otto

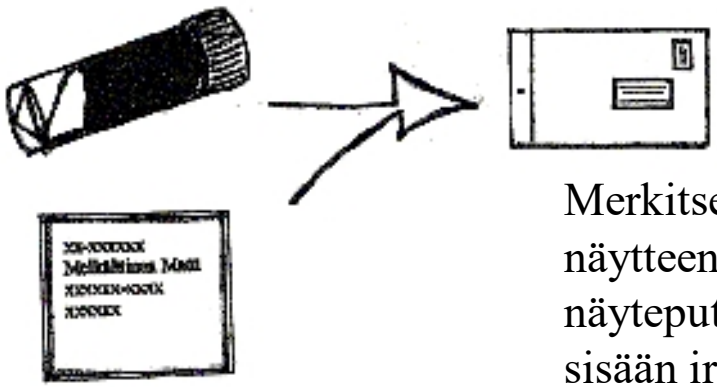


Aseta pahvilautanen tukevasti pottaan tai WC-istuimen sisään



Paina viistopäinen näytteen-ottoputki kakkaan siten, että putken sisään jää mahdollisimman paljon näytettä (käy myös vaipasta otettaviin näytteisiin)

Laita näytteenottoputki kuljetusputken sisään ja ruuvaa korkki tiukasti kiinni



Merkitse henkilötietotarroihin näytteenottopäivä ja laita ne näyteputkien kanssa postituslaatikon sisään irrallisina

16. Notification of Clinic Results

16.1. Autoantibody Results Notification

Notification of autoantibody test (GADA, IA-2A, IAA and ZnT8A (which will be run on selected positive autoantibody samples as determined by the Immune Markers committee, see details below)) results should take place prior to the next scheduled clinic visit. Results should be given within six weeks, but no later than twelve weeks after the blood sample was drawn. The results from the local TEDDY Autoantibody Reference Lab (i.e., Eisenbarth's laboratory in the US and Bingley's laboratory in Europe) should be reported to families. Results are given to the families without confirmation of positive sera by both TEDDY Autoantibody Reference Labs.

16.1.1. DCC Result Reporting

Each TEDDY Autoantibody Reference Lab uses the TEDDY website to upload files containing autoantibody results to the DCC. The DCC imports these results into a database. The DCC notifies each clinical center, by email, of the results of these autoantibody tests.

16.1.2. Training

All TEDDY staff members engaged in direct contact with families must be trained and practiced in results notification and details of the TEDDY follow-up study before contacting participants. Training will occur initially at a centralized training session or at the local sites by approved trainers. Elements of the training will be the same across the life of the study and include:

1) Successful completion of Humans Subjects Protections Training course
2) Reading the Manual of Operations and the Protocol related to follow-up procedures
3) Training in communicating results to families, explaining the meaning of the results, educating parents about diabetes, reviewing the study and it's purpose, inviting parents to ask questions and being prepared with answers to the FAQs.
4) All new staff must listen/observe at least one interaction when positive results are given to the family by an experienced member of the TEDDY project before the new staff member is approved to begin reporting positive autoantibody results alone.

16.1.3. Considerations

1) It is important when reporting results to keep in mind the psychological impact that these results may have on the family and to help relieve any undue stress.
2) Anxious families should first be referred to the lead study coordinator and then to the site PI.
3) Families should be offered additional counseling as necessary.

16.1.4. ZnT8A measurements

If a subject is currently deemed autoantibody positive for GAD, MIAA and/or IA2A (any number of autoantibodies, any autoantibody, persistence or confirmation not required) at current visit, ZnT8A will be run on that autoantibody sample at the Denver lab. Once ZnT8A is run on the autoantibody positive subject, ZnT8A will be run on all future collected samples. ZnT8A will be measured until the subject is autoantibody negative for all 4 autoantibodies for 1 year; at which point ZnT8A would be stopped until autoantibody positivity reappears for the other three autoantibodies (GAD, MIAA and/or IA2A). If a subject is currently or in the future deemed persistent confirmed single or multiple autoantibody positive and/or has developed T1D - ZnT8A will be run on all of the subject's past samples at the Denver lab. If a subject is currently or in the future deemed persistent confirmed single or multiple autoantibody positive and/or has developed T1D - ZnT8A will be run on all of the subject's future samples at the Denver lab.

16.1.5. Reporting Local Laboratory Results to Families

1) In the U.S., results from the Denver laboratory are to be reported to families
2) In Europe, results from the Bristol laboratory and ZnT8A results from the Denver laboratory are to be reported to families
3) Results from the second, reference lab are for study purposes and are not reported to families (except for the ZnT8A results for European subject received from the Denver laboratory)
4) Definitions:
   - Negative = result is within the normal range for the local laboratory
   - Positive = result is above the normal range for the local laboratory
   - Persistent Positive = a positive test result is above the normal range for the local laboratory on subsequent sample(s)
   - Transient Positive = positive on previous sample, but negative on the follow-up sample.

16.1.6. Reporting Negative Autoantibody Results

Negative autoantibody results should be reported via letter. The letter should explain:

1) The autoantibody tests results were normal;
2) There is no change in the child's risk for type 1 diabetes;
3) The child's risk for developing type 1 diabetes, restating the risk using the same natural numbers employed in your initial letter to the child's parent (e.g., 3 out of 100 for general population or 14 out of 100 for first degree relatives in the US);.
4) Autoantibodies may appear in the future;
5) We will continue to test for autoantibodies at the next study visit.

16.1.7. Reporting Positive Autoantibody Results

Positive autoantibody results should be reported via phone conversation and then followed up with a letter.

16.1.7.1. Positive Autoantibody Test Results For the First Time

The script and letter should:

1) Explain the test results for one or more autoantibody tests were positive or above normal;
2) Specify the test results and the normal range;
3) Restate the child's genetic risk for type 1 diabetes using the same natural numbers employed in your initial letter to the child's parent (e.g., 3 out of 100 for general population or 14 out of 100 for first degree relatives in the US);
4) State that the child's positive autoantibody test result indicates that the child's risk for type 1 diabetes may have increased slightly;
5) State that positive autoantibody test results sometimes return to normal levels on subsequent tests;
6) Indicate that we will continue to test for autoantibodies at the next study visit.

16.1.7.2. One Positive Autoantibody Test Result For the ≥Second Time

The script and letter should:

1) Explain the autoantibody test result was positive or above normal more than once;
2) Specify the test results and the normal range;

3) State that the child's ≥ second positive autoantibody test result indicates that the child's risk for type 1 diabetes is increased;
4) Specify that out of 100 children with these test results, 15 will go on to develop type 1 diabetes;
5) Indicate that we will continue to test for autoantibodies and blood glucose levels at the next study visit

16.1.7.3. Multiple Autoantibody Persistent Positive

The script and letter should:

1) Remind the family the child had been positive for an autoantibody previously;
2) Explain the test results show the child is now positive for two or more autoantibody tests.
3) Specify the test results and the normal range;
4) Indicate that the child's risk for type 1 diabetes is significantly increased;
5) State that current scientific studies indicate that out of 100 children with these test results, 70 will go on to develop type 1 diabetes within the next 10 years of the child's life;
6) Provide the signs and symptoms of type 1 diabetes;
7) Recommend the parents contact the child's primary care physician;
8) State that we will continue to test for autoantibodies at the next study visit;
9) State that we will carefully monitor the child for the development of diabetes by testing the child's blood glucose and hemoglobin A1c level every 3 months at their TEDDY study visit and by doing an oral glucose tolerance test every 6 months at a regularly scheduled TEDDY visit.
10) State that diagnosing diabetes early means the child will receive treatment right away and may not need to be hospitalized at the time of diagnosis.

16.1.8. Reporting negative autoantibody results that have previously tested positive for a single autoantibody

Occasionally a positive autoantibody test will test negative on subsequent testing. When this occurs, the participant should be told:

1) Autoantibody results often change over time
2) A negative test does not reduce the child's risk of diabetes.

16.1.9. Reporting negative autoantibody results that have previously tested positive for multiple autoantibodies

In cases with multiple positive autoantibodies, one or more tests may become negative on subsequent testing. When this occurs, the participant should be told:

1) Autoantibody results can change over time
   Although scientists are currently studying such cases, current scientific evidence indicates that a negative test result in a child who has previously tested positive for two or more auto antibodies does not reduce the child's risk of diabetes

Appendix 16 provides model letters and telephone scripts for the more common scenarios.

16.2. Celiac Disease: Transglutaminase autoantibodies

16.2.1 Reporting Transglutaminase Autoantibody Results

Beginning when the child reaches 2 years of age and annually thereafter celiac autoantibodies (tissue transglutaminase) will be measured from the serum sample taken at the clinic visit; the islet autoantibody sample blood volume will be increased to 120 µl for this purpose.

16.2.1.1 Reporting Local Laboratory Results to Families

For TGA samples collected at the US sites the Data Coordinating Center will request the Repository to send TGA samples to the European Reference laboratory for confirmatory testing that are greater than or equal to 0.01 at the US lab. TGA samples collected at the European sites will not be analyzed at the US lab.

1) In the U.S., TGA results from Eisenbarth's laboratory are to be reported to families (the sample test name of these samples is "Transglutaminase Sample (Autoantibody Reference Lab sample)")
2) In Europe, TGA results from Bingley's laboratory are to be reported to families (the sample test name of these samples is "Transglutaminase Sample (Autoantibody Reference Lab sample)")
3) Results from the second reference lab are for study purposes and are not reported to families (the sample test name of these samples is "Transglutaminase Sample (Autoantibody Repository sample)")
4) Definitions:
   - Negative = result is within the normal range for the local laboratory
   - Positive = result is above the normal range for the local laboratory
   - Persistent Positive = a positive test result is above the normal range for the local laboratory on subsequent sample(s)
   - Transient Positive = positive on previous sample, but negative on the follow-up sample.

16.2.1.2 Negative Transglutaminase Autoantibody Results

Negative test results may be given at the next clinic visit, via phone call or letter. If the sample is negative the autoantibodies are analyzed again after one year.

16.2.1.3 Positive Transglutaminase Autoantibody Results

If the annual transglutaminase autoantibody (TGA) sample, which starts at 2 years, is positive, the autoantibodies are analyzed again after 3 months (or 6 months if the child is on the 6 month visit schedule after 4 years of age). If persistently positive, the child will have attained the TEDDY study endpoint for TGA. Persistence is defined as having two consecutive TGA positive samples at any time. Children positive for TGA will continue to be screened annually. Persistently TGA positive children will be referred to their pediatricians for confirmation of diagnosis by an intestinal biopsy and possible initiation of gluten free diet, if clinically indicated. The *Celiac disease information sheet* should be sent to all families with notification of persistent positive TGA, as well as information about family risk of celiac disease.

16.2.1.3.1 Genetic Risk of Siblings of Children Diagnosed with Celiac Disease in TEDDY

In the TEDDY study, the exact HLA-DQ genotype is not shared with participants. Therefore, precise genetic counseling is not practical for close relatives of the TEDDY child. Without giving the HLA-DQ genotype of the proband or without knowing the HLA-DQ genotype of the sibling, it is recommended to inform the parent that there is an average risk of 10% for a sibling to be affected by celiac disease if another child in the family has celiac disease. This information is also given in the Celiac Disease Information sheet to the parents of a child detected with persistently positive tissue transglutaminase autoantibody levels who is referred to the local pediatrician for confirming the celiac disease diagnosis.

16.2.2 Celiac Disease Forms

The TEDDY "Tracking Form: Symptoms of Celiac Disease" should be completed for <u>all</u> children at the 6 month visit, 12 month visit, 18 month visit, 24 month visit and then annually. The "Tracking Form: Symptoms of Celiac Disease" can be found on each subject's Participant's Details Page under each of the visits that the form should be collected at. The information that is collected on the form should be since the last time the form was completed; ask the parent "Since the last time we completed this form, has your child had or is currently having any of the following problems?" If the annual transglutaminase autoantibody sample cannot be collected at the annual visit, but the "Tracking Form: Symptoms of Celiac Disease" can be collected, then collect the information for the Tracking Form at the annual visit. If the information for the Tracking Form cannot be collected until the next visit it is ok to collect it then.

If the subject's annual TGA sample is found to be positive, the TEDDY "Tracking Form: Symptoms of Celiac Disease at Transglutaminase autoantibody persistent visit" should be completed at the next visit. The "Tracking Form: Symptoms of Celiac Disease at Transglutaminase autoantibody persistent visit" can be found on the subject's Participant's Details Page under the next sequential visit after the annual TGA sample was found to be positive at. The information that is collected on the form should be since the last time the form was completed; ask the parent "Since the last time we completed this form, has your child had or is currently having any of the following problems?" If the transglutaminase autoantibody sample cannot be collected at this visit, but the "Tracking Form: Symptoms of Celiac Disease" can be collected, then collect the information for the Tracking Form at the visit. If the information for the Tracking Form cannot be collected until the next visit it is ok to collect it then.

> <u>Note:</u> If the annual TGA sample is not able to be collected until the visit immediately prior to the visit that the next annual sample is due at, the site should not complete a "Tracking Form: Symptoms of Celiac Disease at Transglutaminase autoantibody persistent visit" at the next visit following the TGA positive sample because that visit will be the annual visit that the "Tracking Form: Symptoms of Celiac Disease" will be collected at (forms contain the same questions).

The "Positive Transglutaminase Autoantibody Follow-Up/Biopsy Form" should be completed on all children who have persistent positive TGA (at the 24 month visit and on) or who were

diagnosed with Celiac disease outside of the TEDDY study. Persistence is defined as having two consecutive TGA positive samples at any time (at the 24 month visit and on). If biopsy did occur, then indicate outcome on the form, if no biopsy occurred then document reasons why not. More than one form should be submitted per subject if biopsies have been performed on several occasions or the biopsy data has changed. This form can be found under the "Additional Study Forms" drop-down menu on the Participant's Details Page. The DCC will create a report which lists the subjects who have persistent positive TGA (at the 24 month visit and on) and subjects who were diagnosed with Celiac Disease outside of TEDDY with the diagnosis indicated on the 3 month interview, TEDDY Book extraction form or TEDDY Update Form to help the Clinical Centers determine which subjects need this form completed. The site will know about the Celiac disease diagnosis when the parent indicates Celiac disease in the Chronic Illness section of the TEDDY Book- please note that site should indicate ICD-10 code K90.0 (see section 16.2.2.1.)- and at that time the site should complete the "Positive Transglutaminase Autoantibody Follow-Up/Biopsy Form".

The "Tracking Form: Gluten-free Diet Annual Update Form" will be collected annually on all children who have been diagnosed with Celiac Disease (see section 16.2.2.1.)(regardless if diagnosis occurred as a result of TEDDY or outside of TEDDY) and children who are currently persistent positive TGA (currently persistent TGA positive is defined as having two consecutive TGA positive samples at the last two visits in which TGA was tested). This form can be found on the subject's Participant's Details Page. Once a form has been completed for a subject, the site should continue to complete a new form at every annual visit thereafter. If the subject is persistent TGA positive for a period of time and then tests negative for one year the "Tracking Form: Gluten-free Diet Annual Update Form" will no longer be collected annually (unless the subject becomes persistent positive again). A negative year will be started at the date of collection of the first negative result.

16.2.2.1. Celiac Disease Diagnosis

Celiac disease diagnosis should be confirmed by review of the medical record. If the GI specialist or pediatrician makes a diagnosis of celiac disease it should be recorded in the Chronic Illnesses section of the TEDDY Book as ICD-10 code K90.0. If the doctor suspects celiac disease and/or the parents suspect celiac disease, this is not the same as a diagnosis and should not be recorded in the Chronic Illnesses section. If the subject is on a gluten free diet due to suspected celiac disease, this should be captured in the Special Diets Section of the TEDDY Book and coded as SDM09 or SDM16 as appropriate. The special diet indication does not mean that a "Tracking Form: Gluten free Diet Annual Update Form" or the "Positive Transglutaminase Autoantibody Follow-Up/ Biopsy Form" should be completed. However, these forms should be completed if the subject meets the requirements listed in section 16.2.2.

16.3. Thyroid Peroxidase (TPOA) and Thyroglobulin (ThGA) Autoantibody and TSH Results

TEDDY will test autoantibodies to thyroid peroxidase (TPOA) and thyroglobulin (ThGA):

1. In all children at 8 years of age or at current visit for those older than age 8. Samples from children positive for either thyroid antibody will also be tested for TSH in the same sample.
2. In all children at 14 years of age. Samples from children positive for either thyroid antibody will also be tested for TSH in the same sample.

3. Children positive for TPOA and/or ThGA at the 8 year visit and/or the 14 year visit will have a confirmatory sample draw at the next TEDDY visit, which will be analyzed for TPOA and ThGA only.
4. In children positive for either thyroid autoantibody at a given sample from step 1 or step 2, additional samples previously collected on that individual will be tested for TPO and ThGA autoantibodies sequentially backwards in sampling age to determine the first sample with either thyroid autoantibody.
5. All TEDDY children who have developed diabetes should be analyzed for TPO and ThGA autoantibodies at the time of clinical diagnosis or at the last TEDDY visit prior to diagnosis.

Children who are found to have thyroid autoimmunity with or without elevated TSH will be informed by TEDDY staff and will be referred for medical care outside of TEDDY based on the normal site-specific protocol.

16.3.1. Reporting Laboratory Results to Families

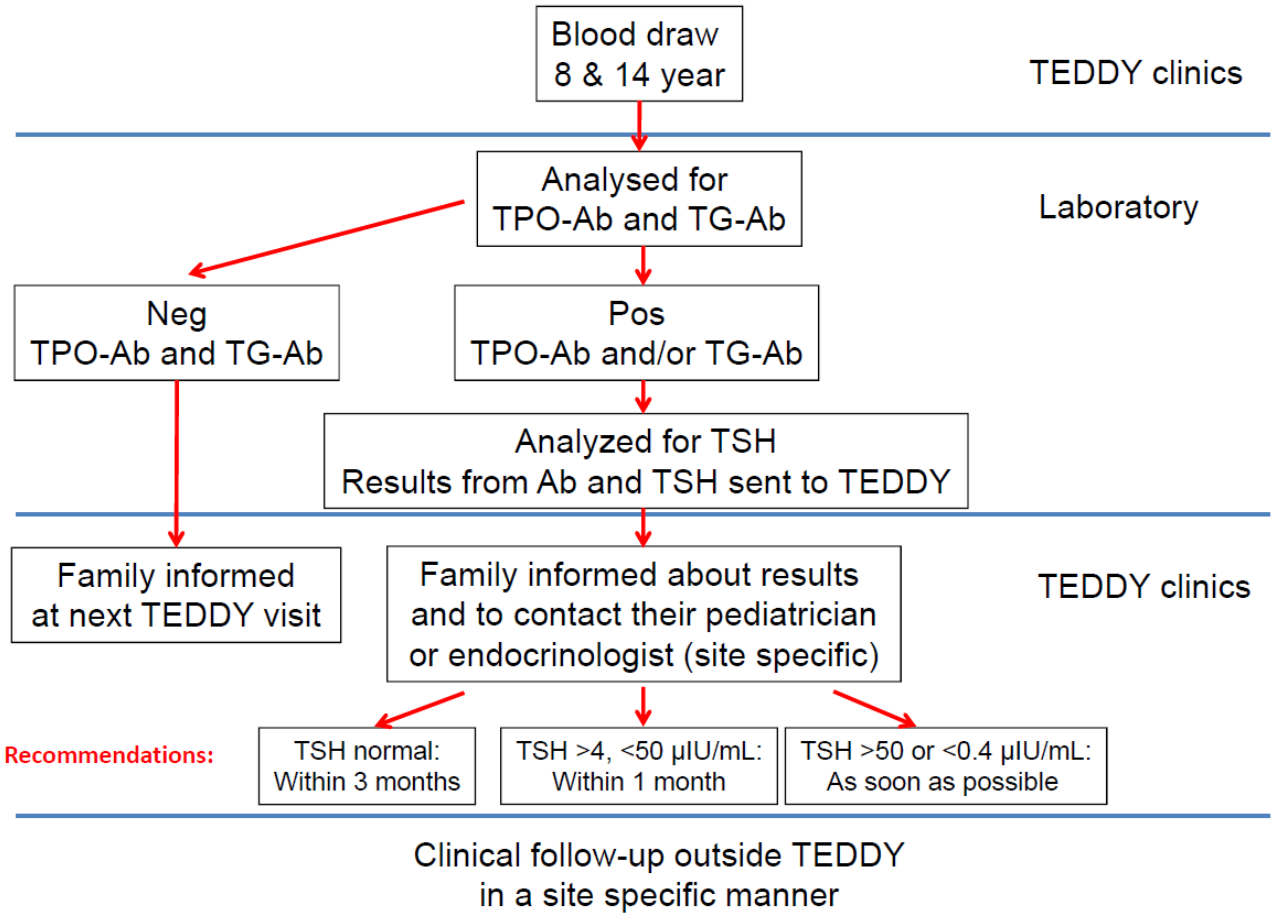
- Negative TPOA and ThGA results: Family will be informed by phone and/or letter, or at the next clinic visit.

- Indeterminate TPOA and ThGA results: For results reporting to families, indeterminate results will be reported as negative results - family will be informed by phone and/or letter, or at the next clinic visit.

- TPOA and/or ThGA results are positive, but TSH normal: The family will be informed about results by phone and/or letter, before a confirmatory sample, and the family will be recommended to contact a pediatrician or endocrinologist (site specific) within 3 months

- Positive TPOA and/or ThGA and TSH >4, <50 μIU/mL: The family will be informed about results by phone and the family will be recommended to contact a pediatrician or endocrinologist (site specific) within 1 month.

- Positive TPOA and/or ThGA and TSH >50 or < 0.4 μIU/mL family informed about results by phone and the family will be recommended to contact a pediatrician or endocrinologist (site specific) within 1 week.



16.4 COVID-19 Antibody Results

Screening for SARS-CoV-2 virus antibodies in TEDDY will enable the study to address the following scientific hypotheses:

Hypothesis 1: The presence of SARS-CoV-2 antibodies is associated with the presence of islet autoantibodies.

Hypothesis 2: Among children positive for islet autoantibodies, those positive also for SARSCoV-2 antibodies (prior to vaccination) will progress faster to clinical diabetes, compared to those negative for SARS-CoV-2 antibodies, controlling for age, sex, race/ethnicity and family history of T1D.

Hypothesis 3: The prevalence of SARS-CoV-2 antibodies will vary by TEDDY clinical center (covering 4 countries) and will increase over time.

The Meso Scale Discovery (MSD) Assay V-PLEX SARS-CoV-2 Panel 2 (IgG) Kit (V-PLEX SARS-CoV-2 Panel 2 (IgG) Kit | Meso Scale Discovery) was selected for use in TEDDY. It is a multiplex serology assay that can be used to measure IgG antibodies to three important antigens related to SARS-CoV-2. The three antigens include: SARS-CoV-2 N, SARS-CoV-2 S1 RBD, and SARS-CoV-2 Spike.

Atlas Genomics in Seattle, Washington (https://atlasresearchlabs.com) was selected to be the COVID-19 antibody testing lab for the TEDDY Study. TEDDY will analyze serum samples from all subjects collected from January 1, 2020 and on. It has been decided that it will be a local decision whether or not the COVID-19 antibody results are reported to the subjects. The Washington and Swedish sites have decided they will report the COVID-19 antibody results to subjects, the other sites have decided not to report these results.

16.5 Automated Emails Identifying Parents and/or TEDDY subjects who underestimate subject's diabetes risk

TEDDY subjects leave the study when they reach 15 years of age. A detailed plan is in place to ease families' transition out of TEDDY. However, two groups of TEDDY subjects are of particular concern: (1) TEDDY teens who have never filled out the First Child Questionnaire or any Annual Child Questionnaire and (2) multiple antibody positive children or their parents who underestimate the child's T1D risk. TEDDY teens who have never filled out a First Child or Annual Child Questionnaire are problematic because we do not know their understanding of their T1D risk. Multiple antibody positive children or their parents who underestimate the child's risk are problematic because underestimating risk in this extremely high-risk group presents a safety concern.

The TEDDY DCC will identify multiple antibody positive children or their parents who underestimate the child's risk at age 13 years and/or 14 years. Sites will be notified about these subjects through an automated email sent by the DCC. The email will contain the following information: Subject ID, Local Code, Clinical Center, Visit Location Code, Child risk perception, Parent(s) risk perception, TEDDY staff ID. To address this underestimation, sites will develop a tailored personalized approach to these families to help ensure adequate understanding of the child's T1D risk.

16.6 Generating TEDDY Results Report (to be given out at 15 year visit)

Clinical Centers will provide subjects with a summary report of their TEDDY study results at the 15 year visit. The results report can be found on the individual subject's Participants Details Page underneath the "Completed Additional Study Forms" box. The Clinical Center will choose the language (English, Finnish, German or Swedish) they want the results report to be printed in and then select "Get Letter". The various language Results Reports can be found in the appendix of this MOO section.

NOTE:

- The 14 year 6 month visit will be the last visit's results that will be used in the Results Report. This ensures that there is enough time to receive the results from the labs and generate the subject's Results Report so that it is ready for use by the 15 year visit.
- The Results Report will be able to be generated by the Clinical Centers three months from the close of the 14 year 6 month window. This ensures that all lab results have been uploaded to the DCC and that the report is ready in time for the first day of the 15 year visit window.
    - The Results Report will only be able to be generated when the 14 year 6 month islet antibody results, 14 year transglutaminase antibody results and 14 year Thyroid antibody results are available or unusable sample status codes are uploaded by the lab or not done reasons are entered in the tracking system by the Clinical Center for all three results.

- "Date of most recent testing" is the date of the last test ran for each of the three types of results (islet antibody, transglutaminase antibody, Thyroid antibody). The date will be the sample collection date of the last sample that was tested for that type.
- If a subject's results do not fit into one of the categories listed below, "Unable to categorize results" will be listed under the corresponding section (Type 1 Diabetes Islet Autoantibodies; Celiac Disease tTG Autoantibody; Autoimmune Thyroid Disease TPO and TG Autoantibodies). The Clinical Centers will address these on a case by case basis.

1. Type 1 Diabetes Islet Autoantibodies	2. Celiac Disease tTG Autoantibody	3.Autoimmune Thyroid Disease TPO and TG Autoantibodies
a. Always Negative b. Previously Single Islet Autoantibody Positive, Most recently Negative c. Most recently Single Islet Autoantibody Positive d. Ever Multiple Islet Autoantibodies Positive	a. Always Negative b. Previously tTGA Positive, most recently Negative c. Most recently tTGA Positive d. Diagnosed with Celiac Disease while in TEDDY	a. Always Negative b. Most recently Autoantibody Positive with Normal TSH c. Most recently Autoantibody Positive with Abnormal TSH d. Diagnosed with Autoimmune Thyroid Disease while in TEDDY

Section 16 – Appendix

A. Model Autoantibody Negative Letter (child's results)
B. Site Specific Autoantibody Negative Letter (child's results)
    1. Colorado (used through August 2014)
    2. Colorado (used starting August 2014)
    3. Finland – only used in Tampere at very beginning of study (never used in Oulu or Turku); *Finland informs by phone and at next visit; does not send a letter*
    4. Germany (used through August 2014)
    5. Germany – FDR (used starting August 2014)
    6. Germany – General Population (used starting August 2014)
    7. Georgia/Florida (used through August 2013)
    8. Georgia/Florida (used August 2013 – September 2014)
    9. Georgia/Florida (used starting September 2014)
    10. Washington (used through August 2014)
    11. Washington (used starting August 2014)
    12. *Sweden informs at next visit; does not send a letter*
C. Model Telephone Script for Reporting First-Time Positive Autoantibody Results (child's results)
D. Model Letter for Reporting First-Time Positive Autoantibody Results (child's results)
E. Site Specific Letter for Reporting First-Time Positive Autoantibody Results (child's results)
    1. Colorado (used through August 2014)
    2. Colorado (used starting August 2014)
    3. Finland – only used in Tampere at very beginning of study (never used in Oulu or Turku); *Finland informs by phone and at next visit; does not send a letter*
    4. Germany
    5. Georgia/Florida (used through August 2013)
    6. Georgia/Florida (used August 2013 – September 2014)
    7. Georgia/Florida (used starting September 2014)
    8. Washington
    9. *Sweden informs at next visit; does not send a letter*
F. Model Letter for Reporting First-Time Multiple Positive Autoantibody Results (child's results)
G. Site Specific Letter for Reporting First-Time Multiple Positive Autoantibody Results (child's results)
    1. Washington
    2. Colorado (used starting August 2014)
H. Model Telephone Script for Reporting Single Persistent Positive Autoantibody Results (child's results)
I. Model Letter for Reporting Single Persistent Positive Autoantibody Results (child's results)
J. Site Specific Letter for Reporting Single Persistent Positive Autoantibody Results (child's results)
    1. Colorado (used starting August 2014)
    2. Germany (used starting August 2014)
    3. Georgia/Florida (used starting September 2014)
    4. Washington (used August 2014 – July 2017)
    5. Washington (used starting July 2017)
K. Site Specific Letter for Reporting ≥ Second-time Positive Autoantibody Results (child's results)
    1. Colorado
    2. Germany
    3. Georgia/Florida (used through August 2013)
    4. Georgia/Florida (used starting in August 2013)
    5. Washington

6. Sweden (used starting September 2014)
7. *Sweden informs at next visit; does not send a letter(up until September 2014)*
8. *Finland informs by phone and at next visit; does not send a letter*

L. Site Specific Letter for Reporting Negative Autoantibody Results When Previous Results Have Been Positive (child's results)
1. Colorado (used through August 2014)
2. Colorado (used starting August 2014)
3. Finland – only used in Tampere at very beginning of study (never used in Oulu or Turku); *Finland informs by phone and at next visit; does not send a letter*
4. Germany
5. Georgia/Florida (used through September 2014)
6. Georgia/Florida (used starting September 2014)
7. Washington
8. *Sweden informs at next visit; does not send a letter*

M. Model Letter for Reporting Negative Autoantibody Results in Cases with a Previous Single Autoantibody Positive Test Result (child's results) – Added to MOO – May 2017

N. Model Telephone Script for Reporting Multiple Persistent Positive Autoantibody Results (child's results) – Edits made to model letter – May 2017

O. Model Letter for Reporting Multiple Persistent Positive Autoantibody Results (child's results) – Edits made to model letter – May 2017

P. Site Specific Letter for Reporting Multiple Persistent Positive Autoantibody Results (child's results)
1. Colorado (used through August 2014)
2. Colorado (used August 2014 – September 2017)
3. Colorado (used starting September 2017)
4. Finland – only used in Tampere at very beginning of study (never used in Oulu or Turku); *Finland informs by phone and at next visit; does not send a letter - started relaying to multiple persistent autoantibody positive subjects that the chance for developing diabetes was 70 out of 100 within 10 years in October 2017*
5. Germany (used through August 2014)
6. Germany (used August 2014 – August 2017)
7. Germany (used starting August 2017)
8. Georgia/Florida (used through August 2013)
9. Georgia/Florida (used August 2013 – September 2014)
10. Georgia/Florida (used September 2014 – November 2017)
11. Georgia/Florida (used starting November 2017)
12. Washington (used August 2014 – July 2017)
13. Washington (used starting July 2017)
14. Sweden (used September 2014 – June 2017)
15. Sweden (used starting June 2017)
16. *Sweden informs at next visit; does not send a letter (up until September 2014)*

Q. Model Letter for Reporting One or More Negative Test Results in Cases with Previous Multiple Persistent Positive Autoantibody Test Results (child's results) – Added to MOO – May 2017

R. Model Multiple Persistent Positive Autoantibody Letter for Physician (child's results) – Edits to model letter – May 2017

S. Site Specific Multiple Persistent Positive Autoantibody Letter for Physician (child's results)
    1. Finland – only used in Tampere at very beginning of study (never used in Oulu or Turku); *Finland informs by phone and at next visit; does not send a letter*
    2. Germany
    3. Georgia/Florida
    4. Washington
    5. *Sweden informs at next visit; does not send a letter*
T. Site Specific Multiple Persistent Positive Antibody to Single Persistent Positive Antibody Letter (for child's results)
    1. Georgia/Florida (used starting September 2014)
U. Model Parent Information Sheet with No Staging Language
V. Site Specific Parent Information Sheet with No Staging Language
    1. Sweden (used starting June 2017)
    2. Finland (used starting September 2017)
W. Model Parent Information Sheet with Staging Language
X. Site Specific Parent Information Sheet with Staging Language
    1. Sweden (used starting June 2017)
Y. TEDDY Diabetes Pamphlet
Z. TEDDY Risk Communication Frequently Asked Questions (FAQs)
AA. Site Specific TEDDY Risk Communications Frequently Asked Questions (FAQs)
    1. Finland (Started using September 2017)
BB. Model Unable to Test for All Autoantibodies due to Insufficient Volume Letter (child's results)
    1. Colorado
CC. Model Maternal Blood Draw Informed Consent Form (for AB testing)
DD. Model Telephone Script for Reporting Maternal Autoantibody Negative Results
EE. Model Telephone Script for Reporting Maternal Autoantibody Positive Results (same marker as infant)
FF. Model Telephone Script for Reporting Maternal Autoantibody Positive Results (different marker than infant)
GG. Model Phone Script For Reporting Positive Celiac Disease Autoantibody Results
HH. Model Celiac Disease Information Sheet
II. Model Letter for Reporting Celiac Test Results
JJ. Site Specific Letter for Reporting Positive Celiac Disease Autoantibody Results
    1. Colorado
    2. Germany
    3. Georgia
    4. Florida
    5. Washington
    6. *Sweden informs at next visit; does not send a letter*
    7. *Finland informs by phone and at next visit; does not send a letter*
KK. Model Letter for Reporting Positive Celiac Disease Autoantibody Results to Pediatric Gastroenterologist
LL. Site Specific Letter for Reporting Negative Celiac Disease Autoantibody Result after a Positive Celiac Disease Autoantibody
    1. Colorado
    2. *Sweden informs at next visit; does not send a letter*
    3. *Finland informs by phone and at next visit; does not send a letter*
MM. Site Specific Letter for Reporting Negative Celiac Disease Autoantibody Results
    1. Colorado

2. Georgia/Florida
3. Washington
4. *Sweden informs at next visit; does not send a letter*
5. *Finland informs by phone and at next visit; does not send a letter*

NN. Site Specific Letter for Reporting Positive Celiac Disease Autoantibody Result after Celiac Disease Diagnosis

1. Colorado
2. *Sweden informs at next visit; does not send a letter*
3. *Finland informs by phone and at next visit; does not send a letter*

OO. Site Specific Letter for Reporting Negative Celiac Disease Autoantibody Result after Celiac Disease Diagnosis

1. Colorado
2. *Sweden informs at next visit; does not send a letter*
3. *Finland informs by phone and at next visit; does not send a letter*

PP. Newsletter, Announcement or Script description of the rational for adding ZnT8A and associated results letters

QQ. Thyroid Staff Sheet

RR. Model Letter for Reporting Thyroid Positive Autoantibody Results (TPOA or ThGa) but TSH is Normal

SS. Model Letter for Reporting Thyroid Positive Autoantibody Results (TPOA or ThGA) and TSH is Borderline

TT. Model Letter for Reporting First-Time Positive Autoantibody Results (TPOA or ThGA) but TSH is Very High or Low

UU. Model Thyroid Autoantibody Negative Letter

VV. Model Positive Thyroid Autoantibody Letter for Physician

WW. TEDDY Results Report – given to family at 15 year visit (English version)

XX. TEDDY Results Report – given to family at 15 year visit (Finnish version)

YY. TEDDY Results Report – given to family at 15 year visit (Swedish version)

ZZ. TEDDY Results Report – given to family at 15 year visit (German version)

AAA. TEDDY Results Report programming requirements

BBB. Site Specific Letter for Reporting Autoantibody Negative Result at 15 year visit

1. Colorado *(will report 15 year Autoantibody positive result by phone)*
2. Germany
3. *Sweden will report 15 year Autoantibody positive and negative results by phone*
4. *Finland will report 15 year Autoantibody positive and negative results by phone*
5. *Georgia will report 15 year Autoantibody positive and negative results by phone*
6. *Washington will report 15 year Autoantibody positive and negative results by phone*

CCC. Site Specific Letter for Reporting Transglutaminase Autoantibody Negative Result at 15 year visit

1. Colorado

DDD. Site Specific Letter for Reporting Results at 15 year visit if subject cannot be reached by phone

1. Sweden

A. MODEL AUTOANTIBODY NEGATIVE LETTER (child's results)

Date

Address

Dear (Parent Contact Name),

We are writing to tell you about your child's latest TEDDY autoantibody test results. This test is done every time we take a blood sample. The presence of autoantibodies is an early signs of an attack on the pancreas.

Your child's latest blood sample did not show any diabetes autoantibodies.
This means there is no change in your child's risk for getting type 1 diabetes at this time.

As you know, every child in the TEDDY study has the diabetes risk genes. This means that your child's risk of developing T1D is much higher than the risk for children born without the diabetes risk genes.

Even though your child's latest blood test showed no diabetes autoantibodies, your child could develop autoantibodies in the future. We expect ___ out of 100 children like yours (___%) will develop type 1 diabetes at some point in the future. (3,3% for gen pop and 14,14% for FDR)

We will continue to test your child at all TEDDY study visits. All tests are provided free of charge.

We will contact you to schedule your next appointment. If you have any questions, please call us at (provide toll free number). Also, please let us know if you have a change of address or phone number.

Thanks so much for taking part in this important study.

Sincerely yours,

Site PI

GRADE LEVEL 6.8

B1a. SITE SPECIFIC AUTOANTIBODY NEGATIVE LETTER: COLORADO (child's results)
(used through August 2014)

Barbara Davis Center for Childhood Diabetes
The University of Colorado at Denver and Health Sciences Center
1775 N. Ursula St
Aurora, Colorado 80045

Parent's Name
Address
Address
TEDDY ID

Dear Parents (or person who signed the informed consent),

We are writing to tell you about the autoantibody test results from (CHILD'S NAME)'s TEDDY study visit on (DATE OF LAST CLINIC VISIT) _____. The results of these tests are **negative**.

This means there is no change in your child's risk for developing type 1 diabetes. As discussed before, we expect 3 out of 100 (14 out of 100) children who have the same genetic test results will develop the disease.

Even though your child's tests were negative at this visit, autoantibodies can appear at anytime in childhood. They usually occur 1 to 2 years before the onset of diabetes. We will continue to test your child at each TEDDY visit. As always, all tests are free of charge and your participation in TEDDY is voluntary.

If you have any questions about these test results or the TEDDY study, please call us at 303-315-0115. We will contact you soon about your next appointment, so please be sure let us know if you have a change of address or phone number.

Thank you for taking part in this diabetes study. We look forward to seeing you at your next clinic visit.

Sincerely,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

B1b. SITE SPECIFIC AUTOANTIBODY NEGATIVE LETTER: COLORADO IN SPANISH
(child's results) (used through August 2014)

Barbara Davis Center for Childhood Diabetes
The University of Colorado at Denver and Health Sciences Center
1775 N. Ursula St
Aurora, Colorado 80045

Parent's Name
Address
Address
TEDDY ID

Estimado Padre de Familia (or person who signed the informed consent),

Le estamos escribiendo para informarle sobre los resultados de las prueba de anticuerpos de (CHILD'S NAME) de la visita TEDDY de (DATE OF LAST CLINIC VISIT) _____. Los resultados de estas pruebas son **negativos**.

Esto significa que no hay cambio en el riesgo de su hijo/a de desarrollar diabetes tipo 1. Como se discutió anteriormente, esperamos que 3 de cada 100 (14 de 100) niños que tienen los mismos resultados de la prueba genética desarrollen la enfermedad.

A pesar de que las pruebas de su hijo/a fueron negativas en esta visita, los anticuerpos pueden aparecer en cualquier momento en la niñez. Usualmente ocurren 1 a 2 años antes del comienzo de la diabetes. Continuaremos analizando a su hijo/a en cada visita TEDDY. Como siempre, todas las pruebas son libres de cobro y su participación en TEDDY es voluntaria.

Si tiene cualquier pregunta sobre los resultados de estas pruebas o el estudio TEDDY, por favor llámenos al 303-315-0115. Lo contactaremos pronto sobre su siguiente cita, así que, por favor déjenos saber si usted cambio de dirección o teléfono.

Gracias por tomar parte en este estudio de diabetes. Esperamos verlo en su próxima visita a la clínica.

Sinceramente,

Marian J. Rewers, MD, PhD
Investigador Principal, Estudio TEDDY

B2a. SITE SPECIFIC AUTOANTIBODY NEGATIVE LETTER: COLORADO (child's results)
(used starting August 2014)

Barbara Davis Center for Diabetes
1775 Aurora Court F527
Aurora, CO 80045

Parent's Name
Address
Address
TEDDY ID

Dear Parents (or person who signed the informed consent),

We are writing to tell you about the autoantibody test results from (CHILD'S NAME)'s TEDDY study visit on (DATE OF LAST CLINIC VISIT) _____. This test is done every time we take a blood sample. The presence of autoantibodies is an early sign of an attack on the pancreas.

Your child's latest blood sample did not show any diabetes autoantibodies. This means there is no change in your child's risk for developing type 1 diabetes. As you know, every child in TEDDY has the higher risk genes for type 1 diabetes. This means your child's risk is greater than the children who do not have these genes.

Even though your child's tests showed no diabetes autoantibodies at this visit, your child could develop autoantibodies in the future. We expect ___out of 100 children like yours will develop type 1 diabetes at some point in the future. (3, 3%, GP, 14, 14% FDR).

Even though your child's tests showed no diabetes autoantibodies at this visit, your child could develop autoantibodies in the future.

We will continue to test your child at each TEDDY visit. As always, all tests are free of charge and your participation in TEDDY is voluntary.

If you have any questions about these test results or the TEDDY study, please call us at 303724.7577. We will contact you soon about your next appointment, so please be sure let us know if you have a change of address or phone number.

Thank you for taking part in this important study. We look forward to seeing you at your next clinic visit.

Sincerely,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

B2b. SITE SPECIFIC AUTOANTIBODY NEGATIVE LETTER: COLORADO IN SPANISH (child's results) (used starting August 2014)

Barbara Davis Center for Diabetes
1775 Aurora Court F527
Aurora, CO 80045

TEDDY

Parent's Name
Address
Address
TEDDY ID

Estimados padres,

Le estamos escribiendo para informarle de los resultados de las pruebas de anticuerpos de (CHILD'S NAME) de la visita TEDDY de (DATE OF LAST CLINIC VISIT) _____. Estas pruebas se hacen cada vez que obtenemos una muestra de sangre. La presencia de autoanticuerpos es una señal temprana de un ataque a los páncreas.

La última muestra de sangre de su hijo/a no mostro ningún autoanticuerpo para la diabetes. Esto significa que no hay cambio en el riesgo que tiene su hijo/a de desarrollar diabetes tipo 1. Como se discutió anteriormente, cada niño en TEDDY tiene un riesgo genético elevado para la diabetes tipo 1. Esto significa que el riesgo de su hijo/a es mayor que aquel de los niños que no tienen estos genes.

A pesar de que los resultados de su hijo/a no mostraron autoanticuerpos para la diabetes en esta visita, su hijo/a puede desarrollar autoanticuerpos en el futuro. Esperamos que ___ de 100 niños como el suyo desarrollen la diabetes tipo 1 en algún punto en el futuro. (3, 3% PG, 14, 14% PDPG).

A pesar de que las pruebas de su hijo/a no mostraron autoanticuerpos para la diabetes en esta visita, su hijo/a puede desarrollar autoanticuerpos en el futuro.

Continuaremos practicándole pruebas a su hijo/a en cada visita de TEDDY. Como siempre, todos los resultados son libres de costo y su participación en TEDDY es voluntaria. Si usted tiene preguntas acerca de estos resultados o acerca del estudio TEDDY, por favor llámenos al 303.724.7577. Pronto nos contactaremos con usted para programar su próxima cita, así que por favor déjenos saber acerca de cualquier cambio a su dirección o su número telefónico.

Gracias por tomar parte de este importante estudio. Esperamos mirarlos pronto en su próxima cita.

Sinceramente,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

AB Negative Letter 8202014

B3. SITE SPECIFIC AUTOANTIBODY NEGATIVE LETTER: FINLAND (child's results)

Hyvät _____:n vanhemmat,

saatte tässä kirjeen lapsenne viimeisimmän TEDDY-käynnin vasta-ainetuloksista. Lapsenne tulokset olivat **negatiiviset.** Tämä tarkoittaa, että lapsenne riski sairastua tyypin 1 diabetekseen ei ole muuttunut.

Jos ajatellaan sellaisia lapsia, joilla on samanlainen peritty diabetesalttius kuin Teidän lapsellanne, noin 7 lasta sadasta sairastuu joskus tyypin 1 diabetekseen.

Vaikka lapsenne vasta-ainetulokset olivat nyt negatiiviset, hänelle saattaa tulevaisuudessa ilmaantua näitä vasta-aineita. Tutkimme nämä vasta-aineet lapseltanne jokaisella TEDDY-käynnillä. Kaikki tutkimukset ovat maksuttomia.

Otamme teihin yhteyttä parin kuukauden kuluttua ja sovimme seuraavan käyntiajan. Jos teillä on jotakin kysyttävää tai haluatte muuten keskustella asioista, soittakaa meille puh._____.

Ilmoittakaa meille, jos osoitteenne tai puhelinnumeronne muuttuu.

Lämpimät kiitoksemme siitä, että osallistutte tähän tärkeään tutkimukseen.

Kunnioittaen

Professori Olli SimellTYKS Lastenklinikka

B4. SITE SPECIFIC AUTOANTIBODY NEGATIVE LETTER: GERMANY (child's results) (used through August 2014)

Brief: negativer AK-Befund

Familie

München, ...

Sehr geehrte Familie .....,

vielen Dank für die Zusendung der Blutprobe vom .....
Die Antikörperuntersuchung bei ..... ergab folgendes Ergebnis:

Antikörpertest	**Normalbereich**	**Antikörperergebnis Ihres Kindes**	**Positiv oder Negativ**
Antiköper IA2	≤ 9 WHO units/ml		
Glutamatdecarboxylase-AK (GADA)	≤ 20 WHO units/ml		
Insulinautoantikörper (Microassay)	≤ 0,95		

Alle Antikörper liegen im Normbereich, d.h. dass sich das Risiko für eine Diabetesentwicklung bei Ihrem Kind nicht erhöht hat. Bei Kindern mit genetischen Anlagen entwickeln 14 (bzw. 3) von 100 Kindern einen Typ 1 Diabetes.

Auch wenn die Antikörperergebnisse diesmal negativ ausgefallen sind, kann Ihr Kind zukünftig Autoantikörper entwickeln. Autoantikörper treten in der Regel 1-2 Jahre vor Ausbruch des Diabetes auf.

Gerne möchten wir auch weiterhin die Antikörper beobachten und, wie besprochen, in drei Monaten einen erneuten Test durchführen. Wir werden uns dann wieder mit Ihnen in Verbindung setzen.

Falls Sie Fragen zum Testergebnis haben, können Sie uns unter der gebührenfreien Telefonnummer 0800 / 33 8 333 9 kontaktieren.

Vielen Dank für Ihre Teilnahme an der TEDDY Studie!

Mit freundlichen Grüßen,

Prof. Dr. Anette-G. Ziegler Dr. med. Peter Achenbach

B5. SITE SPECIFIC AUTOANTIBODY NEGATIVE LETTER: GERMANY - FDR (child's results) (used starting August 2014)

HelmholtzZentrum münchen
Deutsches Forschungszentrum für Gesundheit und Umwelt

Klinikum rechts der Isar

Technische Universität München

Lehrstuhl für Diabetes und Gestationsdiabetes

Institut für Diabetesforschung · Ingolstädter Landstraße 1 · 85764 Neuherberg

Adress

München, 25.11.2014

Sehr geehrte Familie ,

vielen Dank für die Zusendung der Blutprobe.

Die Diabetes-Autoantikörperuntersuchung vom 16.07.2014 bei XY ergab folgendes Ergebnis:

Diabetes-Autoantikörper:				
IAA:	negativ	Titer:	0,00	units (normal <0,95 units)
GADA:	negativ	Titer:	0,00	WHO units/ml (normal <33 WHO units)
IA2A:	negativ	Titer:	0,00	WHO units/ml (normal <5 WHO units)

Alle Diabetes-Autoantikörper liegen im Normbereich. Das bedeutet, dass gegenwärtig keine Inselautoimmunität und kein Typ 1 Diabetes vorliegt.

Das Risiko für Inselautoantikörper und Typ 1 Diabetes wird mit zunehmendem Alter geringer, aber da bei Ihrem Kind zu Beginn der Studie ein erhöhtes genetisches Risiko für Typ 1 Diabetes festgestellt wurde und es bereits Typ 1 Diabetes in Ihrer Familie gibt, ist nicht ausgeschlossen, dass diese Autoantikörper noch in Zukunft auftreten. Eine regelmäßige Kontrolle der Autoantikörper halten wir deshalb bis zum 15. Lebensjahr für sinnvoll.

Forschungsergebnisse zeigen, dass insgesamt etwa 14 von 100 Kindern mit Risikogenen und einem erstgradigen Verwandten mit Typ 1 Diabetes Autoantikörper entwickeln und an Typ 1 Diabetes erkranken.

Gerne möchten wir deshalb auch weiterhin die Autoantikörper, die ein frühes Anzeichen für eine mögliche Diabetesentwicklung darstellen, beobachten und wie besprochen in sechs Monaten einen erneuten Test bei Hannes durchführen. Wir werden uns dann wieder mit Ihnen in Verbindung setzen.

1 von 2

Univ.- Prof. Dr. med. Anette-Gabriele Ziegl
Direktorin
Institut für Diabetesforschung
Helmholtz Zentrum München

und

Forschergruppe Diabetes
Klinikum rechts der Isar
Technische Universität München

Lehrstuhl für Diabetes und Gestationsdiabetes

und

Forschergruppe Diabetes e. V.
am Helmholtz Zentrum München

Vorname, Nachmname, Position

Tel. +49(0)89—3187-xxxx
Fax +49(0)89-3187-3144
vorname.nachname@helmholtz-muenchen.de

Helmholtz Zentrum München
Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH)
Ingolstädter Landstr. 1
85764 Neuherberg
Telefon +49(0)89 3187 (0)
Telefax +49(0)89 3187 3322

info@helmholtz-muenchen.de
www.helmholtz-muenchen.de

Aufsichtsratsvorsitzende:
MinDir'in Bärbel Brumme-Bothe

Geschäftsführer:
Prof. Dr. Günther Wess
Dr. Nikolaus Blum
Dr. Alfons Enhsen

Registergericht:
Amtsgericht München HRB 6466
USt-IdNr- DE 129521671

Bankverbindung:
Münchner Bank eG
Konto-Nr. 2 158 620
BLZ 701 900 00
IBAN DE04701900000002158620
BIC GENODEF1M01

HelmholtzZentrum münchen
Deutsches Forschungszentrum für Gesundheit und Umwelt

Klinikum rechts der Isar

Technische Universität München

Lehrstuhl für Diabetes und Gestationsdiabetes

Wenn Sie Fragen zum Testergebnis oder zur TEDDY-Studie haben, stehen wir Ihnen unter unserer kostenlosen Rufnummer 0800 – 3383339 gerne zur Verfügung.

Vielen Dank für Ihre tolle Mitarbeit an der TEDDY-Studie.

Mit freundlichen Grüßen

Ihre

Prof. Dr. med. Anette-G. Ziegler

Dipl.-Soz. Joanna Stock

Univ.- Prof. Dr. med. Anette-Gabriele Ziegler
Direktorin
Institut für Diabetesforschung
Helmholtz Zentrum München

und

Forschergruppe Diabetes
Klinikum rechts der Isar
Technische Universität München

Lehrstuhl für Diabetes und
Gestationsdiabetes

und

Forschergruppe Diabetes e. V.
am Helmholtz Zentrum München

Vorname, Nachmname, Position

Tel. +49(0)89—3187-xxxx
Fax +49(0)89-3187-3144
vorname.nachname@helmholtz-muenchen.de

Helmholtz Zentrum München
Deutsches Forschungszentrum für
Gesundheit und Umwelt (GmbH)
Ingolstädter Landstr. 1
85764 Neuherberg
Telefon +49(0)89 3187 (0)
Telefax +49(0)89 3187 3322

info@helmholtz-muenchen.de
www.helmholtz-muenchen.de

B6. SITE SPECIFIC AUTOANTIBODY NEGATIVE LETTER: GERMANY – GENERAL POPULATION (child's results) (used starting August 2014)

HelmholtzZentrum münchen
Deutsches Forschungszentrum für Gesundheit und Umwelt

Klinikum rechts der Isar

Technische Universität München

Lehrstuhl für Diabetes und Gestationsdiabetes

Institut für Diabetesforschung · Ingolstädter Landstraße 1 · 85764 Neuherberg

Adress

München, 25.11.2014

Sehr geehrte Familie ,

vielen Dank für die Zusendung der Blutprobe.

Die Diabetes-Autoantikörperuntersuchung vom (Datum) bei XY ergab folgendes Ergebnis:

Diabetes-Autoantikörper:				
IAA:	negativ	Titer:	0,00	units (normal <0,95 units)
GADA:	negativ	Titer:	0,00	WHO units/ml (normal <33 WHO units)
IA2A:	negativ	Titer:	0,00	WHO units/ml (normal <5 WHO units)

Alle Diabetes-Autoantikörper liegen im Normbereich. Das bedeutet, dass gegenwärtig keine Inselautoimmunität und kein Typ 1 Diabetes vorliegt.

Das Risiko für Inselautoantikörper und Typ 1 Diabetes wird mit zunehmendem Alter geringer, aber da bei Ihrem Kind zu Beginn der Studie ein erhöhtes genetisches Risiko für Typ 1 Diabetes festgestellt wurde und es bereits Typ 1 Diabetes in Ihrer Familie gibt, ist nicht ausgeschlossen, dass diese Autoantikörper noch in Zukunft auftreten. Eine regelmäßige Kontrolle der Autoantikörper halten wir deshalb bis zum 15. Lebensjahr für sinnvoll.

Forschungsergebnisse zeigen, dass insgesamt etwa 14 von 100 Kindern mit Risikogenen und einem erstgradigen Verwandten mit Typ 1 Diabetes Autoantikörper entwickeln und an Typ 1 Diabetes erkranken.

Gerne möchten wir deshalb auch weiterhin die Autoantikörper, die ein frühes Anzeichen für eine mögliche Diabetesentwicklung darstellen, beobachten und wie besprochen in sechs Monaten einen erneuten Test bei Hannes durchführen. Wir werden uns dann wieder mit Ihnen in Verbindung setzen.

1 von 2

Univ.- Prof. Dr. med. Anette-Gabriele Ziegler
Direktorin
Institut für Diabetesforschung
Helmholtz Zentrum München

und

Forschergruppe Diabetes
Klinikum rechts der Isar
Technische Universität München

Lehrstuhl für Diabetes und Gestationsdiabetes

und

Forschergruppe Diabetes e. V.
am Helmholtz Zentrum München

Vorname, Nachmname, Position

Tel. +49(0)89—3187-xxxx
Fax +49(0)89-3187-3144
vorname.nachname@helmholtz-muenchen.de

Helmholtz Zentrum München
Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH)
Ingolstädter Landstr. 1
85764 Neuherberg
Telefon +49(0)89 3187 (0)
Telefax +49(0)89 3187 3322

info@helmholtz-muenchen.de
www.helmholtz-muenchen.de

Aufsichtsratsvorsitzende:
MinDir'in Bärbel Brumme-Bothe

Geschäftsführer:
Prof. Dr. Günther Wess
Dr. Nikolaus Blum
Dr. Alfons Enhsen

Registergericht:
Amtsgericht München HRB 6466
USt-IdNr- DE 129521671

Bankverbindung:
Münchner Bank eG
Konto-Nr. 2 158 620
BLZ 701 900 00
IBAN DE04701900000002158620
BIC GENODEF1M01

HelmholtzZentrum münchen
Deutsches Forschungszentrum für Gesundheit und Umwelt

Klinikum rechts der Isar

Technische Universität München

Lehrstuhl für Diabetes und Gestationsdiabetes

Wenn Sie Fragen zum Testergebnis oder zur TEDDY-Studie haben, stehen wir Ihnen unter unserer kostenlosen Rufnummer 0800 – 3383339 gerne zur Verfügung.

Vielen Dank für Ihre tolle Mitarbeit an der TEDDY-Studie.

Mit freundlichen Grüßen

Ihre

Prof. Dr. med. Anette-G. Ziegler

Dipl.-Soz. Joanna Stock

Univ.- Prof. Dr. med. Anette-Gabriele Ziegler
Direktorin
Institut für Diabetesforschung
Helmholtz Zentrum München

und

Forschergruppe Diabetes
Klinikum rechts der Isar
Technische Universität München

Lehrstuhl für Diabetes und
Gestationsdiabetes

und

Forschergruppe Diabetes e. V.
am Helmholtz Zentrum München

Vorname, Nachmname, Position

Tel. +49(0)89—3187-xxxx
Fax +49(0)89-3187-3144
vorname.nachname@helmholtz-muenchen.de

Helmholtz Zentrum München
Deutsches Forschungszentrum für
Gesundheit und Umwelt (GmbH)
Ingolstädter Landstr. 1
85764 Neuherberg
Telefon +49(0)89 3187 (0)
Telefax +49(0)89 3187 3322

info@helmholtz-muenchen.de
www.helmholtz-muenchen.de

Aufsichtsratsvorsitzende:
MinDir'in Bärbel Brumme-Bothe

Geschäftsführer:
Prof. Dr. Günther Wess
Dr. Nikolaus Blum
Dr. Alfons Enhsen

Registergericht:
Amtsgericht München HRB 6466
USt-IdNr- DE 129521671

Bankverbindung:
Münchner Bank eG
Konto-Nr. 2 158 620
BLZ 701 900 00
IBAN DE04701900000002158620
BIC GENODEF1M01

B7. SITE SPECIFIC AUTOANTIBODY NEGATIVE LETTER: GEORGIA/FLORIDA (child's results) (used through August 2013)

Center for Biotechnology and Genomic Medicine

Date

Address

Medical College of Georgia
GEORGIA'S HEALTH SCIENCES UNIVERSITY

TEDDY
Center for Biotechnology and Genomic Medicine
Medical College of Georgia
1120 15th Street, CA-4124
Augusta, GA 30912-2400

Tel: ***1-888-225-7785***
Tel: ***706-721-4161***
Fax: ***706-721-3688***
Email: ***help@pandastudy.org***

Dear (Parent Contact Name),

We are writing to tell you about your child's last TEDDY autoantibody test results. Your child's results were negative. This means there is no change in your child's risk for developing type 1 diabetes.

Among children with your child's genetic test results, we expect ___(3 for US general population; 14 for US FDR) out of 100 children will develop type 1 diabetes.

Even though your child's autoantibody tests were negative, your child could develop autoantibodies in the future. Autoantibodies usually occur 1-2 years before diabetes onset. We will test your child at all TEDDY study visits. All tests are provided free of charge.

We will contact you to schedule your next appointment. If you have any questions, please call us toll free at 1-888-225-7785. Also, please let us know if you have a change of address or phone number.

Thanks so much for taking part in this important study.

Sincerely yours,

B8. SITE SPECIFIC AUTOANTIBODY NEGATIVE LETTER: GEORGIA/FLORIDA (child's results) (used August 2013 – September 2014)

GRU
GEORGIA REGENTS UNIVERSITY
AUGUSTA

Georgia Regents University
Medical College of Georgia
Center for Biotechnology and Genomic Medicine

TEDDY
Center for Biotechnology and Genomic Medicine
Medical College of Georgia
1120 15th Street, CA-4124
Augusta, GA 30912-2400

Tel: 1-888-225-7785
Tel: 706-721-4161
Fax: 706-721-3688

Date

Address

Dear (Parent Contact Name),

We are writing to tell you about your child's last TEDDY antibody test results. Your child's results were negative. This means there is no change in your child's risk for developing type 1 diabetes.

Among children with your child's genetic test results, we expect ___(3 for US general population; 14 for US FDR) out of 100 children will develop type 1 diabetes.

Even though your child's antibody tests were negative, your child could develop antibodies in the future. Antibodies usually occur 1-2 years before diabetes onset. We will test your child at all TEDDY study visits. All tests are provided free of charge.

We will contact you to schedule your next appointment. If you have any questions, please call us toll free at 1-888-225-7785. Also, please let us know if you have a change of address or phone number.

Thanks so much for taking part in this important study.

Sincerely yours,

Diane Hopkins, MS, CCRC
TEDDY Study Project Manager

B9. SITE SPECIFIC AUTOANTIBODY NEGATIVE LETTER: GEORGIA/FLORIDA (child's results) (used starting September 2014)

Georgia Regents University
Medical College of Georgia
Center for Biotechnology and Genomic Medicine

TEDDY
Center for Biotechnology and Genomic Medicine
Georgia Regents University
1120 15th Street, CA-4124
Augusta, GA 30912-2400

Tel: 1-888-225-7785
Tel: 706-721-4161
Fax: 706-721-3688

Date

Address

Dear (Parent Contact Name),

We are writing to tell you about your child's latest TEDDY autoantibody test results. This test is done every time we take a blood sample. Autoantibodies are early signs of an attack on the pancreas.

Your child's latest blood sample did not show any diabetes autoantibodies.. This means there is no change in your child's risk for developing type 1 diabetes at this time.

As you know, every child in the TEDDY study has the diabetes risk genes. This means that your child's risk of developing T1D is much higher than the risk for children born without the diabetes risk genes.

Even though your child's latest blood test showed no diabetes autoantibodies,, your child could develop autoantibodies in the future. We expect ___(3 for US general population; 14 for US FDR) out of 100 children like yours (___%) will develop type 1 diabetes at some point in the future.

We will continue to test your child at all TEDDY study visits. All tests are provided free of charge.

We will contact you to schedule your next appointment. If you have any questions, please call us toll free at 1-888-225-7785. Also, please let us know if you have a change of address or phone number.

Thanks so much for taking part in this important study.

Sincerely yours,

Diane Hopkins, MS, CCRC
TEDDY Study Project Manager

B10. SITE SPECIFIC AUTOANTIBODY NEGATIVE LETTER: WASHINGTON (child's results) (used through August 2014)

PACIFIC NORTHWEST DIABETES RESEARCH INSTITUTE
720 Broadway • Seattle, Washington 98122 • 206-726-1200 • www.pndri.org

Parent Doe
123 Main Street
Anytown, WA 98123

Dear _____,

This is to report the test results from your last TEDDY study clinic visit. We'd like to thank you for taking part in this important study.

_____ tested **negative** for autoantibody risk markers of childhood diabetes. This news is reassuring. There is no guarantee, but the results suggest that your child is not developing diabetes.

Even though your child tested negative for autoantibodies, the markers can appear later in childhood. In general, they show up one or more years before a child gets diabetes. A child may develop diabetes without having the markers, but this is rare. The most common age to get childhood diabetes is 12. We will continue to test your child at their next clinic visit in 3 months. All tests are provided completely free of charge, and your participation is entirely voluntary.

Someone from our research team will contact you in about 2 months to schedule your appointment. If you have any questions before we contact you again, or if you do not wish to participate in the future, please feel free to contact us at 1-888-324-2140. Also, please contact us if you have a change of address or phone number.

Sincerely yours,

William A. Hagopian, MD, PhD,
Principal Investigator, Northwest TEDDY Study
Pacific NW Research Institute
206-860-6770
Toll Free: 1-888-324-2140

B11. SITE SPECIFIC AUTOANTIBODY NEGATIVE LETTER: WASHINGTON (child's results) (used starting August 2014)

PACIFIC NORTHWEST DIABETES RESEARCH INSTITUTE
720 Broadway • Seattle, Washington 98122 • 206-726-1200 • www.pndri.org

Date

Address

Dear (Parent Contact Name),

We are writing to tell you about <child's name>'s latest TEDDY autoantibody test results. This test is done every time we take a blood sample. The presence of autoantibodies is an early sign of an attack on the pancreas.

<Child's name>'s latest blood sample did not show any diabetes autoantibodies.
This means there is no change in your child's risk for getting type 1 diabetes at this time.

As you know, every child in the TEDDY study has the diabetes risk genes. This means that your child's risk of developing T1D is much higher than the risk for children born without the diabetes risk genes.

Even though your child's latest blood test showed no diabetes autoantibodies, your child could develop autoantibodies in the future. We expect out of 100 children like yours (___%) will develop type 1 diabetes at some point in the future. <3,3% for gen pop and 14,14% for FDR>

We will continue to test your child at all TEDDY study visits. All tests are provided free of charge.

We will contact you to schedule your next appointment.

If you have any questions, please call us toll free at 1-888-324-2140. Also, please let us know if you have a change of address or phone number.

Thanks so much for taking part in this important study.

Sincerely yours,

Site PI

GRADE LEVEL 6.8

A-1 Negative Autoantibody Letter Revised 4/7/2014

C. MODEL TELEPHONE SCRIPT FOR REPORTING FIRST-TIME POSITIVE AUTOANTIBODY RESULTS (child's results)

Hello, my name is _____ and I am calling from the TEDDY Study. May I speak with _____ (parent/legal guardian of TEDDY child)? Do you have a few minutes to talk?"

[If yes, continue]

[If no, record when to re-call and then say goodbye.]

Do you remember we took some blood from your child at the last TEDDY study visit? We use this blood to test for three kinds of autoantibodies. Testing for autoantibodies is another way we have to look at your child's risk for developing type 1 diabetes. Most children develop autoantibodies one or more years before they get diabetes.

Two of your child's autoantibody test results were negative or normal. However, your child's _____(specify autoantibody) test result was _____ which is above normal levels. When a test result is above normal, we describe the test result as "positive." This means that your child's risk for type 1 diabetes may be slightly increased. Please do not be alarmed. This does NOT mean your child will definitely get diabetes.

Among children with your child's genetic test results, we expect ___(3 for US general population; 14 for US FDR; European sites need to specify their numbers by country) out of 100 children will develop type 1 diabetes**.** Your child's positive _____ (specify autoantibody) test result suggests that your child's risk for type 1 diabetes may be slightly higher than this number. This does NOT mean your child will get diabetes for sure. Sometimes positive autoantibody test results return to normal when the child is tested a second time. When your child comes in for the next TEDDY study visit, we will test your child's autoantibodies again and let you know the results.

Do you have any questions or concerns that I can answer at this time? **[If parents seem overly concerned, go over the numbers again, and address any concerns. If needed, offer to put them in contact with PI or counselor.]**

We will be sending you a letter describing your child's autoantibody test results. If you have any questions or concerns, please call us on our toll free number _____.

Your next TEDDY study visit is scheduled for _____(provide data and time). We look forward to seeing you then.

GRADE LEVEL: 7.7

D. MODEL LETTER FOR REPORTING FIRST-TIME POSITIVE AUTOANTIBODY RESULTS
(child's results)

Parent Doe
123 Main Street
Anytown, WA 98123

Dear _____,

This is a follow-up letter to the telephone call we had about your child's autoantibody test results. Your child's test results are listed below.

Name of Autoantibody Test	Normal Level – TEDDY Assay (US Sites)	Normal Level – TEDDY Assay (European Sites)	Normal Level– Harmonized Assay (US Sites)	Normal Level– Harmonized Assay (European Sites)	Your Child's Results	Positive or Negative
IA-2A	≤ 0.03 [index] – NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤ 9 WHO units/ml - NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤5	<5		
GADA	≤ 0.032 [index] - – NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤ 20 WHO units/ml - – NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤20	<33		
IAA	≤ 0.01 [index]	≤ 0.95 [index]	No harmonized assay; TEDDY assay will continue to be used	No harmonized assay; TEDDY assay will continue to be used		
ZnT8A	≤ 0.020					

Two of your child's test results were negative or normal. However, one of your child's test results was positive or above normal. This means that your child's risk for type 1 diabetes may be slightly increased. This does NOT mean your child will definitely get diabetes.

Among children with your child's genetic test results, we expect ___(3 for US general population; 14 for US FDR; European sites need to specify their numbers by country) out of 100 children will develop type 1 diabetes**.** One positive autoantibody test result suggests that your child's risk for type 1 diabetes may be slightly higher than this number. This does NOT mean your child will get diabetes for sure. Sometimes positive autoantibody test results return to normal when the child is tested a second time. When your child

comes in for the next TEDDY study visit, we will test your child's autoantibodies again and let you know the results.

If you have any questions or concerns, please call us on our toll free number _____.

Your next TEDDY study visit is scheduled for _____(provide data and time). We look forward to seeing you then.

Thanks so much for your participation in this important study.

Sincerely yours,

Site PI

GRADE LEVEL: 7.7

E1a. SITE SPECIFIC LETTER FOR REPORTING FIRST-TIME POSITIVE AUTOANTIBODY RESULTS: COLORADO (child's results) (used through August 2014)

Barbara Davis Center for Childhood Diabetes
The University of Colorado at Denver and Health Sciences Center
1775 N. Ursula St
Aurora, Colorado 80045

Parent's Name
Address
Address
TEDDY ID

Dear Parents (or person who signed the informed consent),

Thank you for taking the time to speak with us about (CHILD'S NAME) autoantibody test results. As we talked about on the phone, your child's autoantibody test results from the (DATE OF LAST CLINIC VISIT) visit are listed below.

Autoantibody Test	Your Child's Result	Normal Level	Meaning
IA-2/ICA 512	+0.000	<	positive
GAD65	-0.000	<	negative
IAA	-0.000	<	negative

Two of your child's test results were negative or normal. However, one of the test results was positive or above normal. It does NOT mean your child will definitely get diabetes.

Among children with your child's genetic test results, we expect 3 out of 100 (14 of 100) children will develop type 1 diabetes**. W**ith one positive autoantibody test your child's risk may be slightly increased. Sometimes autoantibody test results return to normal. We will continue to test your child at each TEDDY visit. As always, all tests are free of charge and taking part in TEDDY is voluntary.

If you have any questions about these test results or the TEDDY study, please call us at 303-315-0115 We will contact you soon about your next appointment, so please let us know if you have a change in address or phone number.

Thank you for taking part in this study. We look forward to seeing you at your next visit.

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

E1b. SITE SPECIFIC LETTER FOR REPORTING FIRST-TIME POSITIVE AUTOANTIBODY RESULTS: COLORADO IN SPANISH (child's results) (used through August 2014)

Barbara Davis Center for Childhood Diabetes
The University of Colorado at Denver and Health Sciences Center
1775 N. Ursula St
Aurora, Colorado 80045

Parent's Name
Address
Address
TEDDY ID

Estimado Padre de Familia (or person who signed the informed consent),

Gracias por tomarse el tiempo de hablar con nosotros sobre los resultados de la prueba de anticuerpos de (CHILD'S NAME). Como hablamos con usted por teléfono, los resultados de la prueba de anticuerpos de su hijo/a de la visita del (DATE OF LAST CLINIC VISIT) se listan a continuación.

Prueba Anticuerpo	Los resultados de su Hijo/a	Nivel Normal	Significado
IA-2/ICA 512	+0.000	<	positivo
GAD65	-0.000	<	negativo
IAA	-0.000	<	negativo

Uno o más de los resultados de la prueba fueron positivos o arriba de lo normal. NO significa que su hijo/a definitivamente vaya adquirir diabetes.

La base del riesgo genético de que su hijo/a desarrolle diabetes tipo 1 es de 3 de cada 100 (14 de 100) cuando se unió al estudio TEDDY. Los resultados de la prueba de anticuerpos positivos indican que el riesgo su hijo/a pueda tener un ligero incremento. Algunas veces los resultados de la prueba regresan a normal. Continuaremos haciendo revisiones a su hijo/a en cada visita TEDDY. Como siempre, todas las pruebas son libres de cobro y formar parte de TEDDY es voluntario.

Si tiene cualquier pregunta sobre estos resultados o el Estudio TEDDY. Por favor llámenos al 303-315-0115. Pronto lo/la contactaremos para su próxima cita, así que, por favor déjenos saber si ha cambiado de dirección o numero de teléfono.

Gracias por formar parte de este estudio. Esperamos verlo/a en su próxima visita.

Marian J. Rewers, MD, PhD
Investigador Principal, Estudio TEDDY

E2a. SITE SPECIFIC LETTER FOR REPORTING FIRST-TIME POSITIVE AUTOANTIBODY RESULTS: COLORADO (child's results) (used starting August 2014)

Dear Parents,

Thank you for taking the time to speak with us about JANE's antibody test results. As we talked about on the phone, your child's antibody test results drawn on 1/11/2010 are listed below.

Antibody Test	Your child's result	Normal Level	Meaning
GAD65	0.039	<= 0.032	Positive
IA-2	-0.002	<= 0.03	Negative
IAA	0.005	<= 0.01	Negative

One or more of your child's test results was positive or above normal. This means that the risk for type 1 diabetes may be increased. It does NOT mean your child will definitely get diabetes.

Among children with the same genetic test results, we expect ___(3 for US general population; 14 for US FDR) out of 100 children will develop type 1 diabetes**.** More than one positive autoantibody test result suggests that «childs_name»'s risk for type 1 diabetes may be higher than this number. Sometimes positive autoantibody test results return to normal when the child is tested a second time.

We will continue to test your child at each TEDDY visit. As always, all tests are free of charge and taking part in TEDDY is voluntary.

If you have any questions about these test results or the TEDDY study, please call us at 303-724-7577. We will contact you soon about your next appointment. Please let us know if you have a change of address or phone number.

Thank you for taking part in this important study. We look forward to seeing you at your next clinic visit.

Sincerely,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

E2b. SITE SPECIFIC LETTER FOR REPORTING FIRST-TIME POSITIVE AUTOANTIBODY RESULTS: COLORADO IN SPANISH (child's results) (used starting August 2014)

Estimados Padres,

Gracias por tomarse el tiempo de hablar con nosotros acerca de los resultados de las pruebas de anticuerpos de (CHILD'S NAME). Como hablamos con usted por teléfono, los resultados de la prueba de anticuerpos de su hijo/a de la visita de (date) son los siguientes:

Prueba Anticuerpo	Los resultados de su hijo/a	Nivel Normal	Significado
GAD65	0.039	<= 0.032	Positivo
IA-2	-0.002	<= 0.03	Negativo
IAA	0.005	<= 0.01	Negativo

Uno o más de los resultados de las pruebas de su hijo/a fueron positivos o arriba de lo normal. Esto significa que el riesgo para la diabetes tipo 1 puede aumentar. Esto NO significa que su hijo/a definitivamente desarrollé diabetes.

Entre los niños con los mismos resultados de pruebas genéticas como su hijo/a, esperamos que___ (3 para la población general de EE.UU.; 14 para los PDPG en EE.UU.) de 100 niños desarrollaran diabetes tipo 1. Más de un resultado positivo de autoanticuerpo sugiere que el riesgo de «childs_name» puede ser más alto que este número. Algunas veces los resultados de pruebas positivas regresan a la normalidad cuando al niño/a se le hace la prueba una segunda vez.

Continuaremos haciendo revisiones a su hijo/a en cada visita de TEDDY. Como siempre, todas las pruebas son libres de cobro y la participación en el estudio es voluntaria.

Si usted tiene alguna pregunta acerca de los resultados de estas pruebas o del estudio TEDDY, por favor llame al 303-724-7577. Pronto nos contactaremos con usted para programas su próxima cita, así que, por favor déjenos saber si hay algún cambio a su dirección o número telefónico.

Gracias por tomar parte de este importante estudio. Esperamos verlo/a en su próxima visita.

Sinceramente,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

AB1stTime1orMore8202014

E3. SITE SPECIFIC LETTER FOR REPORTING FIRST-TIME POSITIVE AUTOANTIBODY RESULTS: FINLAND (child's results)

Hyvät _____:n vanhemmat,

saitte jo etukäteen puhelimitse tiedon lapsenne vasta-ainetuloksista. Tulokset on lueteltu alla:

Vasta-ainetutkimus	***Normaaliarvo***	**Lapsenne tulos**	**Positiivinen tai negatiivinen**
ICA 512	alle		
GAD	alle		
IAA	alle		

Kaksi lapsenne vasta-ainetuloksista oli negatiivisia eli normaaleja, mutta **yksi tulos oli positiivinen** eli normaalia korkeampi. Tämä tarkoittaa, että lapsenne riski sairastua diabetekseen saattaa olla hieman suurentunut. On kuitenkin täysin mahdollista, ettei lapsenne koskaan sairastu diabetekseen.

Jos ajatellaan sellaisia lapsia, joilla on samanlainen diabeteksen riskigeenitulos kuin Teidän lapsellanne, noin 7 lasta sadasta sairastuu joskus tyypin 1 diabetekseen. Yksi positiivinen vasta-ainetulos viittaa siihen, että Teidän lapsenne riski sairastua diabetekseen saattaa olla hieman tätä suurempi. Joskus positiivinen vasta-ainetulos muuttuu normaaliksi, kun lapsi tutkitaan uudelleen.

Kun lapsenne tulee seuraavalle TEDDY-käynnille, tutkimme hänen vasta-ainetasonsa uudelleen ja tiedotamme teille tuloksista. Jos teillä on jotakin kysyttävää tai haluatte muuten keskustella asioista, soittakaa meille puh._____.

Tervetuloa seuraavalle TEDDY-käynnillenne _____.

Lämpimät kiitoksemme siitä, että osallistutte tähän tärkeään tutkimukseen.

Kunnioittaen

Professori Olli Simell
TYKS Lastenklinikka

E4. SITE SPECIFIC LETTER FOR REPORTING FIRST-TIME POSITIVE AUTOANTIBODY RESULTS: GERMANY (child's results)

Brief: erstmals positiv

Familie .....

München, 26.01.24

Sehr geehrte Familie .....,

die Antikörperuntersuchung vom ..... bei Ihrem Kind ..... (geb. .....) ergab folgende Werte:

Antikörpertest	**Normalbereich**	**Antikörperergebnis Ihres Kindes**	**Positiv oder Negativ**
Antiköper IA2	≤ 9 WHO units/ml		
Glutamatdecarboxylase-AK (GADA)	≤ 20 WHO units/ml		
Insulinautoantikörper (Microassay)	≤ 0,95		

Wie bereits telefonisch besprochen, waren zwei der drei Antikörpertests negativ, d.h. normal. Ein Antikörperergebnis war positiv d.h. über dem Normalwert. Ein positiver Antikörperwert deutet darauf hin, dass das Risiko für Typ 1 Diabetes bei Ihrem Kind leicht erhöht ist. Es bedeutet nicht, dass Ihr Kind in jedem Fall Diabetes entwickeln wird. Bei Kindern mit genetischen Anlagen entwickeln 14 (bzw. 3) von 100 Kindern einen Typ 1 Diabetes.

Ein positives Antikörperergebnis kann bei der nächsten Untersuchung normal ausfallen. Wenn Ihr Kind zur nächsten Blutentnahme geht, werden wir wieder die Antikörper untersuchen und Ihnen das Ergebnis mitteilen.

Falls Sie Fragen haben, können Sie uns unter der gebührenfreien Telefonnummer 0800 / 33 8 333 9 kontaktieren.

Vielen Dank für Ihre Teilnahme an der TEDDY Studie!
Mit freundlichen Grüßen,
Prof. Dr. Anette-G. Ziegler
Dr. med. Peter Achenbach

E5. SITE SPECIFIC LETTER FOR REPORTING FIRST-TIME POSITIVE AUTOANTIBODY RESULTS: GEORGIA/FLORIDA (child's results) (used through August 2013)

Medical College of Georgia
GEORGIA'S HEALTH SCIENCES UNIVERSITY
Center for Biotechnology and Genomic Medicine

TEDDY
Center for Biotechnology and Genomic Medicine
Medical College of Georgia
1120 15th Street, CA-4124
Augusta, GA 30912-2400

Tel: ***1-888-225-7785***
Tel: ***706-721-4161***
Fax: ***706-721-3688***
Email: ***help@pandastudy.org***

Date

Address

Dear (Parent Contact Name),

This is a follow-up letter to the telephone call we had about your child's autoantibody test results. Your child's test results are listed below.

Name of Autoantibody Test	Normal Level (US Sites)	Normal Level (European Sites)	Your Child's Results	Positive or Negative
IA-2A	≤ 0.03 [index]	≤ 9 WHO units/ml		
GADA	≤ 0.032 [index]	≤ 20 WHO units/ml		
IAA	≤ 0.01 [index]	≤ 0.95 [index]		

Two of your child's test results were negative or normal. However, one of your child's test results was positive or above normal. This means that your child's risk for type 1 diabetes may be slightly increased. This does NOT mean your child will definitely get diabetes.

Among children with your child's genetic test results, we expect ___(3 for US general population; 14 for US FDR) out of 100 children will develop type 1 diabetes**.** One positive autoantibody test result suggests that your child's risk for type 1 diabetes may be slightly higher than this number. This does NOT mean your child will get diabetes for sure. Sometimes positive autoantibody test results return to normal when the child is tested a second time. When your child comes in for the next TEDDY study visit, we will test your child's autoantibodies again and let you know the results.

If you have any questions or concerns, please call us at our toll free number _____.

Your next TEDDY study visit is scheduled for _____(provide data and time). We look forward to seeing you then.

Thanks so much for your participation in this important study.

Sincerely yours,

E6. SITE SPECIFIC LETTER FOR REPORTING FIRST-TIME POSITIVE AUTOANTIBODY RESULTS: GEORGIA/FLORIDA (child's results) (used August 2013 – September 2014)

Georgia Regents University
Medical College of Georgia
Center for Biotechnology and Genomic Medicine

TEDDY
Center for Biotechnology and Genomic Medicine
Medical College of Georgia
1120 15th Street, CA-4124
Augusta, GA 30912-2400

Tel: 1-888-225-7785
Tel: 706-721-4161
Fax: 706-721-3688

Date

Address

Dear (Parent Contact Name),

This is a follow-up letter to the telephone call we had about your child's antibody test results. Your child's test results are listed below.

Name of Autoantibody Test	Normal Level	Your Child's Results	Positive or Negative
IA-2A	≤ 0.03		
GADA	≤ 0.032		
IAA	≤ 0.01		
ZnT8A	≤ 0.020		

TEDDY tests for four different autoantibodies. One or more of your child's latest test results was positive or above normal. This means that your child's risk for type 1 diabetes may be slightly increased. This does NOT mean your child will definitely get diabetes.

Among children with your child's genetic test results, we expect ___(3 for US general population; 14 for US FDR) out of 100 children will develop type 1 diabetes. A positive antibody test result suggests that your child's risk for type 1 diabetes may be slightly higher than this number. This does NOT mean your child will get diabetes for sure. Sometimes positive antibody test results return to normal when the child is tested a second time. When your child comes in for the next TEDDY study visit, we will test your child's antibodies again and let you know the results.

If you have any questions or concerns, please call us at our toll free number _____.

Thanks so much for your participation in this important study.

Sincerely yours,

Diane Hopkins, MS, CCRC
TEDDY Study Project Manager

E7. SITE SPECIFIC LETTER FOR REPORTING FIRST-TIME POSITIVE AUTOANTIBODY RESULTS: GEORGIA/FLORIDA (child's results) (used starting September 2014)

GRU
GEORGIA REGENTS UNIVERSITY
AUGUSTA

Georgia Regents University
Medical College of Georgia
Center for Biotechnology and Genomic Medicine

TEDDY
Center for Biotechnology and Genomic Medicine
Georgia Regents University
1120 15th Street, CA-4124
Augusta, GA 30912-2400

Tel: 1-888-225-7785
Tel: 706-721-4161
Fax: 706-721-3688

Date

Address

Dear (Parent Contact Name),

This is a follow-up letter to the telephone call we had about your child's autoantibody test results. Your child's test results are listed below.

Name of Autoantibody Test	Normal Level	Your Child's Results	Positive or Negative
IA-2A	≤ 0.03		
GADA	≤ 0.032		
IAA	≤ 0.01		
ZnT8A	≤ 0.020		

TEDDY tests for four different autoantibodies. One or more of your child's latest test results was positive or above normal. This means that your child's risk for type 1 diabetes may be slightly increased. This does NOT mean your child will definitely get diabetes.

Among children with your child's genetic test results, we expect ___(3 for US general population; 14 for US FDR) out of 100 children will develop type 1 diabetes. A positive autoantibody test result suggests that your child's risk for type 1 diabetes may be slightly higher than this number. This does NOT mean your child will get diabetes for sure. Sometimes positive autoantibody test results return to normal when the child is tested a second time. When your child comes in for the next TEDDY study visit, we will test your child's autoantibodies again and let you know the results.

If you have any questions or concerns, please call us at our toll free number _____.

Thanks so much for your participation in this important study.

Sincerely yours,

Diane Hopkins, MS, CCRC
TEDDY Study Project Manager

Version Date: 9/15/2014

E8. SITE SPECIFIC LETTER FOR REPORTING FIRST-TIME POSITIVE AUTOANTIBODY RESULTS: WASHINGTON (child's results)

PACIFIC NORTHWEST DIABETES RESEARCH INSTITUTE
720 Broadway • Seattle, Washington 98122 • 206-726-1200 • www.pndri.org

<Date>

<Parent Name>
<Address>
<City, WA 98123>

Dear _____(Parent),

This is a follow-up letter to the telephone call we had about your child's autoantibody test results. Your child's test results are listed below.

Name of Autoantibody Test	Normal Level	Your Child's Results	Positive or Negative
IA-2A	≤ 5		
GADA	≤ 20		
IAA	≤ 0.01		
ZnT8	≤ 0.020		

Three of your child's test results were negative or normal. However, one of your child's test results was positive or above normal. This means that your child's risk for type 1 diabetes may be slightly increased. This does NOT mean your child will definitely get diabetes.

Among children with your child's genetic test results, we expect <____ (3 (gen pop) or 14 (FDR)> out of 100 children will develop type 1 diabetes**.** One positive autoantibody test result suggests that your child's risk for type 1 diabetes may be slightly higher than this number. This does NOT mean your child will get diabetes for sure. Sometimes positive autoantibody test results return to normal when the child is tested a second time. When your child comes in for the next TEDDY study visit, we will test your child's autoantibodies again and let you know the results.

If you have any questions or concerns, please call us on our toll free number 1-888-324-2140.

Thanks so much for your participation in this important study.

Sincerely yours,
Investigator who reported results

F. MODEL LETTER FOR REPORTING FIRST-TIME MULTIPLE POSITIVE AUTOANTIBODY RESULTS (child's results)

Parent Doe
123 Main Street
Anytown, WA 98123

Dear _____,

This is a follow-up letter to the telephone call we had about «childs_name»'s autoantibody test results. The results are listed below.

Name of Autoantibody Test	Normal Level – TEDDY Assay (US Sites)	Normal Level – TEDDY Assay (European Sites)	Normal Level– Harmonized Assay (US Sites)	Normal Level– Harmonized Assay (European Sites)	Your Child's Results	Positive or Negative
IA-2A	≤ 0.03 [index] – NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤ 9 WHO units/ml - NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤5	<5		
GADA	≤ 0.032 [index] - – NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤ 20 WHO units/ml - – NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤20	<33		
IAA	≤ 0.01 [index]	≤ 0.95 [index]	No harmonized assay; TEDDY assay will continue to be used	No harmonized assay; TEDDY assay will continue to be used		
ZnT8A	≤ 0.020					

More than one of the test results was positive or above normal. This means that the risk for type 1 diabetes may be increased. This does NOT mean «childs_name» will definitely get diabetes.

Among children with the same genetic test results, we expect ___(3 for US general population; 14 for US FDR; European sites need to specify their numbers by country) out of 100 children will develop type 1 diabetes**.** More than one positive autoantibody test result suggests that «childs_name»'s risk for type 1 diabetes may be higher than this number. This does NOT mean **he/she** will get diabetes for sure. Sometimes positive autoantibody test results return to normal when the child is tested a second time. When «childs_name» comes in for the next TEDDY study visit, we will test for autoantibodies again and let you know the results.

Your next TEDDY study visit is scheduled for _____. We look forward to seeing you then – but please don't hesitate to call at any time if you have any questions.

Sincerely yours,

Site PI

G1. SITE SPECIFIC LETTER FOR REPORTING FIRST-TIME MULTIPLE POSITIVE AUTOANTIBODY RESULTS: WASHINGTON (CHILD'S RESULTS)

<Date>

<Parent Doe>
<123 Main Street>
<Anytown, WA 98123>

Dear _____,

This is a follow-up letter to the telephone call we had about <**child's name's>** autoantibody test results. The results are listed below.

Name of Autoantibody Test	Normal Level	Your Child's Results	Positive or Negative
IA-2A	≤ 5		
GADA	≤ 20		
IAA	≤ 0.01		
ZnT8	≤ 0.020		

More than one of the test results were positive or above normal. This means that your child's risk for type 1 diabetes is increased. This does NOT mean <**child's name>** will definitely get diabetes.

Among children with the same genetic test results, we expect <**___(3 for US general population; 14 for US FDR**)> out of 100 children will develop type 1 diabetes**.** More than one positive autoantibody test result suggests that <**child's name's>** risk for type 1 diabetes may be even higher. This does NOT mean your child will get diabetes for sure. Sometimes positive autoantibody test results return to normal when the child is tested a second time. When **<child's name>** comes in for the next TEDDY study visit, we will test for autoantibodies again and let you know the results.

If you have any questions or concerns, please call our toll free number at 1-888-324-2140.

Thanks so much for your participation in this important study.

Sincerely yours,

Investigator who reported results

G2A. SITE SPECIFIC LETTER FOR REPORTING FIRST-TIME MULTIPLE POSITIVE AUTOANTIBODY RESULTS: COLORADO (CHILD'S RESULTS) (USED STARTING AUGUST 2014)

Dear Parents,

Thank you for taking the time to speak with us about JANE's antibody test results. As we talked about on the phone, your child's antibody test results drawn on 1/11/2010 are listed below.

Antibody Test	Your child's result	Normal Level	Meaning
GAD65	0.039	<= 0.032	Positive
IA-2	-0.002	<= 0.03	Negative
IAA	0.005	<= 0.01	Negative

One or more of your child's test results was positive or above normal. This means that the risk for type 1 diabetes may be increased. It does NOT mean your child will definitely get diabetes.

Among children with the same genetic test results, we expect ___(3 for US general population; 14 for US FDR) out of 100 children will develop type 1 diabetes**.** More than one positive autoantibody test result suggests that «childs_name»'s risk for type 1 diabetes may be higher than this number. Sometimes positive autoantibody test results return to normal when the child is tested a second time.

We will continue to test your child at each TEDDY visit. As always, all tests are free of charge and taking part in TEDDY is voluntary.

If you have any questions about these test results or the TEDDY study, please call us at 303-724-7577. We will contact you soon about your next appointment. Please let us know if you have a change of address or phone number.

Thank you for taking part in this important study. We look forward to seeing you at your next clinic visit.

Sincerely,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

G2B. SITE SPECIFIC LETTER FOR REPORTING FIRST-TIME MULTIPLE POSITIVE AUTOANTIBODY RESULTS: COLORADO IN SPANISH(CHILD'S RESULTS) (USED STARTING AUGUST 2014)

Estimados Padres,

Gracias por tomarse el tiempo de hablar con nosotros acerca de los resultados de las pruebas de anticuerpos de (CHILD'S NAME). Como hablamos con usted por teléfono, los resultados de la prueba de anticuerpos de su hijo/a de la visita de (date) son los siguientes:

Prueba Anticuerpo	Los resultados de su hijo/a	Nivel Normal	Significado
GAD65	0.039	<= 0.032	Positivo
IA-2	-0.002	<= 0.03	Negativo
IAA	0.005	<= 0.01	Negativo

Uno o más de los resultados de las pruebas de su hijo/a fueron positivos o arriba de lo normal. Esto significa que el riesgo para la diabetes tipo 1 puede aumentar. Esto NO significa que su hijo/a definitivamente desarrollé diabetes.

Entre los niños con los mismos resultados de pruebas genéticas como su hijo/a, esperamos que___ (3 para la población general de EE.UU.; 14 para los PDPG en EE.UU.) de 100 niños desarrollaran diabetes tipo 1. Más de un resultado positivo de autoanticuerpo sugiere que el riesgo de «childs_name» puede ser más alto que este número. Algunas veces los resultados de pruebas positivas regresan a la normalidad cuando al niño/a se le hace la prueba una segunda vez.

Continuaremos haciendo revisiones a su hijo/a en cada visita de TEDDY. Como siempre, todas las pruebas son libres de cobro y la participación en el estudio es voluntaria.

Si usted tiene alguna pregunta acerca de los resultados de estas pruebas o del estudio TEDDY, por favor llame al 303-724-7577. Pronto nos contactaremos con usted para programas su próxima cita, así que, por favor déjenos saber si hay algún cambio a su dirección o número telefónico.

Gracias por tomar parte de este importante estudio. Esperamos verlo/a en su próxima visita.

Sinceramente,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

AB1stTime1orMore8202014

H. MODEL TELEPHONE SCRIPT FOR REPORTING SINGLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS (child's results)

Hello, my name is _____ and I am calling from the TEDDY Study. May I speak with _____ (parent/legal guardian of TEDDY child)? Do you have a few minutes to talk?"

[If yes, continue]

[If no, record when to re-call and then say goodbye.]

We have called you about your child's autoantibody test results before. Remember that on the _____ (date or dates) TEDDY study visit (s), your child's test results were positive for the _____ (specify type) autoantibody. We talked about the results by phone and we sent you a letter(s) describing the results.

Today I am calling about the results from your child's last TEDDY study visit. Your child's _____(specify autoantibody) test result was _____ which is above normal. This means that your child continues to test positive for the _____(specify autoantibody).

Since your child has tested positive more than once, your child's risk for type 1 diabetes has increased. This does NOT mean your child will definitely get diabetes.

Based on these results, we estimate your child's risk of getting type 1 diabetes to be 15%. We want to stress that a positive autoantibody test result does NOT mean your child will get diabetes for sure. Not all children with positive autoantibody test results go on to get type 1 diabetes. When your child comes in for the next TEDDY study visit, we will test your child's autoantibodies again and let you know the results.

Do you have any questions or concerns that I can answer at this time? **[If parents seem overly concerned, go over the numbers again, and address any concerns. If needed, offer to put them in contact with PI or counselor.]**

We will be sending you a letter describing your child's autoantibody test results. If you have any questions or concerns, please call us on our toll free number _____.

Your next TEDDY study visit is scheduled for _____(provide data and time). We look forward to seeing you then.

GRADE LEVEL: 7.2

I. MODEL LETTER FOR REPORTING SINGLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS (child's results)

Date

Address

Dear (Parent Contact Name),

This is a follow-up letter to the telephone call we had about your child's autoantibody test results. Your child's test results are listed below.

Name of Autoantibody Test	Normal Level – TEDDY Assay (US Sites)	Normal Level – TEDDY Assay (European Sites)	Normal Level– Harmonized Assay (US Sites)	Normal Level– Harmonized Assay (European Sites)	Your Child's Results	Positive or Negative
IA-2A	≤ 0.03 [index] – NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤ 9 WHO units/ml - NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤5	<5		
GADA	≤ 0.032 [index] - – NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤ 20 WHO units/ml - – NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤20	<33		
IAA	≤ 0.01 [index]	≤ 0.95 [index]	No harmonized assay; TEDDY assay will continue to be used	No harmonized assay; TEDDY assay will continue to be used		
ZnT8A	≤ 0.020					

Three of your child's test results were negative or normal. However, one of your child's test results was positive or above the normal level. Your child has tested positive for a diabetes autoantibody more than once.

Based on these results, we estimate your child's risk of getting diabetes to be 15%. This means that out of 100 children with these test results, it is likely that 15 will develop type 1diabetes.

This does NOT mean your child will get diabetes for sure. When your child comes in for the next TEDDY study visit, we will test your child's diabetes autoantibodies and blood glucose levels.

If you have any questions or concerns, please call us on our toll free number _____.

Thanks so much for your participation in this important study.

Sincerely yours,

GRADE LEVEL 7.4

J1a. SITE SPECIFIC LETTER FOR REPORTING SINGLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: COLORADO (CHILD'S RESULTS) (used starting August 2014)

Dear Parents,
This is a follow-up letter to the telephone call we had about your child's autoantibody test results. Your child's test results are listed below.

Antibody Test	Your Child's Result	Normal Level	Meaning
GAD65	2	≤ 20	Negative
IA-2	1	≤ 5	Negative
IAA	0.02	≤ 0.01	Positive
Znt8		<0.020	Negative

Three of your child's test results were negative or normal. However, one of the test results was positive or above the normal level. Your child has tested positive for a diabetes autoantibody more than once.

Based on these results, we estimate your child's risk of getting diabetes to be 15%. This means that out of 100 children with these test results, it is likely that 15 will develop type 1 diabetes.

This does NOT mean your child will definitely get diabetes. We will continue to test your child's autoantibodies and blood glucose level at each TEDDY visit. As always, all tests are free of charge and taking part in TEDDY is voluntary.

If you have any questions about these test results, please call us at 303-724.7577. We will contact you soon about your next appointment so please be sure to let us know if you have a change of address or phone number.

Thank you for taking part in the TEDDY study. We look forward to seeing you at your next clinic visit.

Sincerely,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

J1b. SITE SPECIFIC LETTER FOR REPORTING SINGLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: COLORADO IN SPANISH (CHILD'S RESULTS) (used starting August 2014)

Estimados padres,
Esta es una carta de seguimiento a la llamada que tuvimos con usted acerca de los resultados de los autoanticuerpos de su hijo/a. Los resultados de su hijo/a son los siguientes:

Prueba Anticuerpo	Resultados de su hijo/a	Nivel Normal	Significado
GAD65	2	≤ 20	Negativo
IA-2	1	≤ 5	Negativo
IAA	0.02	≤ 0.01	Positivo
Znt8		<0.020	Negativo

Tres de las pruebas de su hijo/a son negativas o normales. Sin embargo, uno de los resultados de las pruebas fue positivo o arriba de lo normal. Su hijo a dado positivo para un autoanticuerpo para la diabetes más de una vez.

Basado en estos resultados, estimamos que el riesgo de su hijo de desarrollar diabetes es 15%. Esto significa que de 100 niños con estos resultados, es posible que 15 de ellos desarrollen diabetes tipo1.

Esto NO significa que su hijo/a definitivamente desarrolle diabetes. Continuaremos haciendo pruebas a los autoanticuerpos de su hijo/a al igual que haremos pruebas del nivel de azúcar en la sangre de su hijo/a en cada visita de TEDDY. Como siempre, todas las pruebas son libres de costo y tomar parte de este estudio es voluntario.

Si tiene preguntas acerca de estos resultados, por favor llame al 303-724-7577. Pronto nos contactaremos con usted para programar su próxima cita, así que por favor déjenos saber si hay algún cambio en su dirección o en su número telefónico.

Gracias por tomar parte de este importante estudio. Esperamos mirarlos en su siguiente visita.

Sinceramente,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

SingleAbPosPersistent 8202014

J2. SITE SPECIFIC LETTER FOR REPORTING SINGLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: GERMANY (CHILD'S RESULTS) (used starting August 2014)

HelmholtzZentrum münchen
Deutsches Forschungszentrum für Gesundheit und Umwelt

Klinikum rechts der Isar

Technische Universität München

Lehrstuhl für Diabetes und Gestationsdiabetes

Institut für Diabetesforschung · Ingolstädter Landstraße 1 · 85764 Neuherberg

Univ.- Prof. Dr. med. Anette-Gabriele Ziegler
Direktorin
Institut für Diabetesforschung
Helmholtz Zentrum München

und

Forschergruppe Diabetes
Klinikum rechts der Isar
Technische Universität München

Lehrstuhl für Diabetes und
Gestationsdiabetes

und

Forschergruppe Diabetes e. V.
am Helmholtz Zentrum München

Vorname Nachname
Position

Tel. +49(0)89-3187-xxxx
Fax +49(0)89-3187-3144
vorname.nachname@helmholtz-muenchen.de

München, 25.11.2014

Sehr geehrte Familie,

vielen Dank für die Zusendung der Blutprobe.

Die Antikörperuntersuchung vom (Datum) bei xxx ergab folgendes Ergebnis:

Diabetes-Autoantikörper:

IAA:	negativ	0,00	units (normal < 0,95 units)
GADA :	negativ	2,38	WHO units/ml (normal < 33 WHO units)
IA2A:	positiv	99,62	WHO units/ml (normal < 5 WHO units)

Wie bereits telefonisch besprochen, hat sich die Positivität eines der Diabetes-Autoantikörper bei xxx bestätigt. Ein positiver Autoantikörper ist mit keinem wesentlich erhöhten Risiko für einen Typ 1 Diabetes verbunden. Andere Antikörper können sich allerdings in den nächsten Monaten bis Jahren entwickeln. Deshalb ist es wichtig, dass wir diesen Befund mit Hilfe der nächsten Untersuchung im Rahmen von TEDDY in ca. drei Monaten weiterhin beobachten.

Die Wahrscheinlichkeit, dass sich weitere Autoantikörper bilden, ist vor allem in den ersten 5 Jahren nach Auftreten des ersten Autoantikörpers erhöht.

Wenn Sie Fragen zum Testergebnis oder zur TEDDY-Studie haben, stehen wir Ihnen unter folgender kostenlosen Rufnummer 0800 – 3383339 zur Verfügung.

Vielen Dank für Ihre tolle Mitarbeit an unserer TEDDY-Studie.

Mit freundlichen Grüßen

Ihre

Prof. Dr. med. Anette-G. Ziegler Joanna Stock

Helmholtz Zentrum München
Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH)
Ingolstädter Landstr. 1
85764 Neuherberg
Telefon +49(0)89 3187 (0)
Telefax +49(0)89 3187 3322

info@helmholtz-muenchen.de
www.helmholtz-muenchen.de

Aufsichtsratsvorsitzende:
MinDir'in Bärbel Brumme-Bothe

Geschäftsführer:
Prof. Dr. Günther Wess
Dr. Nikolaus Blum
Dr. Alfons Enhsen

Registergericht:
Amtsgericht München HRB 6466
USt-IdNr- DE 129521671

Bankverbindung:
Münchner Bank eG
Konto-Nr. 2 158 620
BLZ 701 900 00
IBAN DE04701900000002158620
BIC GENODEF1M01

1 von 1

J3. SITE SPECIFIC LETTER FOR REPORTING SINGLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: GEORGIA/FLORIDA (CHILD'S RESULTS) (used starting September 2014)

Georgia Regents University
Medical College of Georgia
Center for Biotechnology and Genomic Medicine

TEDDY
Center for Biotechnology and Genomic Medicine
Georgia Regents University
1120 15th Street, CA-4124
Augusta, GA 30912-2400

Tel: 1-888-225-7785
Tel: 706-721-4161
Fax: 706-721-3688

Date

Address

Dear (Parent Contact Name),

This is a follow-up letter to the telephone call we had about your child's autoantibody test results. Your child's test results are listed below.

Name of Autoantibody Test	Normal Level	Your Child's Results	Positive or Negative
IA-2A	≤ 0.03		
GADA	≤ 0.032		
IAA	≤ 0.01		
ZnT8A	< 0.020		

Three of your child's test results were negative or normal. However, one of your child's test results was positive or above the normal level. Your child has tested positive for a diabetes autoantibody more than once.

Based on these result, we estimate your child's risk of getting diabetes to be about 15%. This means that out of 100 children with these test results, it is likely that 15 will develop type 1 diabetes.

This does NOT mean your child will get diabetes for sure. When your child comes in for the next TEDDY study visit, we will test your child's autoantibodies and blood glucose levels.

If you have any questions or concerns, please call us on our toll free number _____.

Thanks so much for your participation in this important study.

Sincerely yours,

Diane Hopkins, MS, CCRC
Version Date: 9/15/2014

J4. SITE SPECIFIC LETTER FOR REPORTING SINGLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: WASHINGTON (CHILD'S RESULTS) (used August 2014 – July 2017)

PACIFIC NORTHWEST DIABETES RESEARCH INSTITUTE
720 Broadway • Seattle, Washington 98122 • 206-726-1200 • www.pndri.org

Date

Address

Dear (Parent Contact Name),

This is a follow-up letter to the telephone call we had about <child's name>'s autoantibody test results. Your child's test results are listed below.

Name of Autoantibody Test	Normal Level	Your Child's Results	Positive or Negative
IA-2A	≤ 5		
GADA	< 20		
IAA	≤ 0.01		
ZnT8A	≤ 0.020		

Three of <child's name>'s test results were negative or normal. However, one of your child's test results was positive or above the normal level. Your child has tested positive for a diabetes autoantibody more than once.

Based on these results, we estimate your child's risk of getting diabetes to be 15%. This means that out of 100 children with these test results, it is likely that 15 will develop type 1diabetes.

This does NOT mean your child will get diabetes for sure. When your child comes in for the next TEDDY study visit, we will test your child's diabetes autoantibodies and blood glucose levels.

If you have any questions or concerns, please call us on our toll free number 1-888-324-2140.

Thanks so much for your participation in this important study.

Sincerely yours,

Investigator Reporting Results

GRADE LEVEL 7.4

A-5 Single Persistent Autoantibody Letter Revised 4/7/2014

J5. SITE SPECIFIC LETTER FOR REPORTING SINGLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: WASHINGTON (CHILD'S RESULTS) (used starting in July 2017)

#16176098.0

PACIFIC NORTHWEST DIABETES RESEARCH INSTITUTE
720 Broadway • Seattle, Washington 98122 • 206-726-1200 • www.pndri.org

Date

Address

Dear (Parent Contact Name),

This is a follow-up letter to the telephone call we had about <child's name>'s autoantibody test results. Your child's test results are listed below.

Name of Autoantibody Test	Normal Level	Your Child's Level	Results
IA-2A	≤ 5		
GADA	≤ 20		
IAA	≤ 0.01		
ZnT8A	≤ 0.020		
HbA1c	≤6.0		

Three of <child's name>'s test results were negative or normal. However, one of your child's test results was positive or above the normal level. Your child has tested positive for a diabetes autoantibody more than once.

Based on these results, we estimate your child's risk of getting diabetes to be 15%. This means that out of 100 children with these test results, it is likely that 15 will develop type 1diabetes.

This does NOT mean your child will get diabetes for sure. When your child comes in for the next TEDDY study visit, we will continue to test your child's diabetes autoantibodies and blood glucose levels.

If you have any questions or concerns, please call us on our toll-free number 1-888-324-2140.

Thanks so much for your participation in this important study.

Sincerely yours,

Investigator Reporting Results

GRADE LEVEL 7.8

K1a. SITE SPECIFIC LETTER FOR REPORTING ≥ SECOND POSITIVE AUTOANTIBODY RESULTS: COLORADO (child's results)

Barbara Davis Center for Childhood Diabetes
The University of Colorado at Denver and Health Sciences Center
1775 N. Ursula St
Aurora, Colorado 80045

Parent's Name
Address
Address
TEDDY ID

Dear Parents (or person who signed the informed consent),

Thank you for taking the time to speak with us about (CHILD'S NAME) autoantibody test results. As we talked about on the phone, your child's autoantibody test results from the (DATE OF LAST CLINIC VISIT) visit are listed below.

Autoantibody Test	Your Child's Result	Normal Level	Meaning
IA-2/ICA 512	+0.000	<	positive
GAD65	-0.000	<	negative
IAA	-0.000	<	negative

Two of your child's test results were negative or normal. However, one of the test results was positive or above normal. Your child has tested positive for one or more autoantibodies previously. It does NOT mean your child will definitely get diabetes.

Your child's baseline genetic risk for developing type 1 diabetes was 3 out of 100 (14 of 100) when you joined the TEDDY Study**.** Your child has tested positive for one or more autoantibodies at this visit and at a previous visit which indicates that your child's risk for type 1 diabetes has increased**.** We will test your child's autoantibodies and blood glucose level at each TEDDY visit. As always, all tests are free of charge and taking part in TEDDY is voluntary.

If you have any questions about these test results or the TEDDY study, please call us at 303-315-0115. We will contact you soon about your next appointment, so please let us know if you have a change in address or phone number.

Thank you for taking part in this study. We look forward to seeing you at your next visit.

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

K1b. SITE SPECIFIC LETTER FOR REPORTING ≥ SECOND POSITIVE AUTOANTIBODY RESULTS: COLORADO IN SPANISH (child's results)

Barbara Davis Center for Childhood Diabetes
The University of Colorado at Denver and Health Sciences Center
1775 N. Ursula St
Aurora, Colorado 80045

Parent's Name
Address
Address
TEDDY ID

Estimado Padre de Familia (or person who signed the informed consent),

Gracias por tomarse el tiempo de hablar con nosotros sobre los resultados de la prueba de anticuerpos de (CHILD NAME). Como hablamos por teléfono, los resultados de la prueba de su hijo/a de la visita de (DATE OF LAST CLINIC VISIT) se listan a continuación.

Prueba Anticuerpos	Resultados de su hijo/a	Nivel Normal	Significado
IA-2/ICA 512	+0.000	<	positivo
GAD65	-0.000	<	negativo
IAA	-0.000	<	negativo

Dos resultados de las pruebas de su hijo/a fueron negativos o normales. De cualquier manera, uno de los resultados fue positivo a arriba de lo normal. Su hijo/a previamente ha tenido positivo a uno a mas de los anticuerpos. NO significa que su hijo/a definitivamente vaya a adquirir diabetes.

La base del riesgo genético de desarrollar diabetes tipo 1 es de 3 de cada 100 (14 de 100) cuando se unió al Estudio TEDDY**.** Su hijo/a sido positivo para uno o más anticuerpos en esta visita y en previas citas el cual indica que el riesgo de diabetes tipo 1 ha incrementado. Estaremos analizando los anticuerpos y nivel de glucosa en la sangre en cada visita TEDDY. Y como siempre, las pruebas son libres de costo y formar parte de TEDDY es voluntario.

Si tiene cualquier pregunta sobre los resultados de estas pruebas o el Estudio TEDDY por favor llámenos al 303-315-0115. Nos contactaremos con usted pronto para su próxima cita, así que, por favor déjenos saber si cambio de dirección o numero de teléfono.

Gracias por formar parte en este estudio de diabetes. Esperamos verlo en su próxima visita a la clínica.
Sinceramente,
Marian J. Rewers, MD, PhD
Investigador Principal, Estudio TEDDY

K2. SITE SPECIFIC LETTER FOR REPORTING ≥ SECOND POSITIVE AUTOANTIBODY RESULTS: GERMANY (child's results)

Brief: Bestätigung eines positiven AK

Familie

München, ...

Sehr geehrte Familie .....,

die Antikörperuntersuchung vom ..... bei Ihrem Kind ..... (geb. .....) ergab folgende Werte:

Antikörpertest	**Normalbereich**	**Antikörperergebnis Ihres Kindes**	**Positiv oder Negativ**
Antiköper IA2	≤ 9 WHO units/ml		
Glutamatdecarboxylase-AK (GADA)	≤ 20 WHO units/ml		
Insulinautoantikörper (Microassay)	≤ 0,95		

Wie bereits telefonisch besprochen, waren zwei der drei Antikörpertests negativ, d.h. normal. Ein Antikörperergebnis war positiv, d.h. über dem Normalwert. Die Positivität für diesen Antikörper hat sich bestätigt.
Da Ihr Kind für diesen Antikörper zum zweiten mal positiv getestet wurde, besteht ein erhöhtes Risiko für Ihr Kind an Diabetes zu erkranken. Bei Kindern mit genetischen Anlagen entwickeln 14 (bzw 3) von 100 Kindern einen Typ 1 Diabetes. Das bedeutet nicht, dass Ihr Kind in jedem Fall Diabetes entwickeln wird.
Ein positives Antikörperergebnis kann bei der nächsten Untersuchung negativ ausfallen. Wenn Ihr Kind zur nächsten Blutentnahme geht, werden wir wieder die Antikörper untersuchen und Ihnen das Ergebnis mitteilen.

Falls Sie Fragen haben, können Sie uns unter der gebührenfreien Telefonnummer 0800 / 33 8 333 9 kontaktieren.

Vielen Dank für Ihre Teilnahme an der TEDDY Studie!

Mit freundlichen Grüßen,

Prof. Dr. Anette-G. Ziegler Dr. med. Peter Achenbach

K3. SITE SPECIFIC LETTER FOR REPORTING ≥ SECOND POSITIVE AUTOANTIBODY RESULTS: GEORGIA/FLORIDA (child's results) (used through August 2013)

Medical College of Georgia
GEORGIA'S HEALTH SCIENCES UNIVERSITY
Center for Biotechnology and Genomic Medicine

TEDDY
Center for Biotechnology and Genomic Medicine
Medical College of Georgia
1120 15th Street, CA-4124
Augusta, GA 30912-2400

Tel:1-888-225-7785
Tel:706-721-4161
Fax:706-721-3688
Email:help@pandastudy.org

Date

Address

Dear (Parent Contact Name),

This is a follow-up letter to the telephone call we had about your child's autoantibody test results. Your child's test results are listed below.

Name of Autoantibody Test	Normal Level (US Sites)	Normal Level (European Sites)	Your Child's Results	Positive or Negative
IA-2A	≤ 0.03 [index]	≤ 9 WHO units/ml		
GADA	≤ 0.032 [index]	≤ 20 WHO units/ml		
IAA	≤ 0.01 [index]	≤ 0.95 [index]		

Two of your child's test results were negative or normal. However, one of your child's test results was positive or above the normal level. Your child has tested positive for this autoantibody more than once.

Among children with your child's genetic test results, we expect _____ (3 for US GP, 14 for US FDR) out of 100 children will develop type 1 diabetes. Because your child has tested positive for this autoantibody more than once this indicates that your child's risk for type 1 diabetes has increased. This does NOT mean your child will get diabetes for sure. When your child comes in for the next TEDDY study visit, we will test your child's autoantibodies and blood glucose levels.

If you have any questions or concerns, please call us on our toll free number _____.

Your next TEDDY study visit is scheduled for _____(provide data and time). We look forward to seeing you then.
Thanks so much for your participation in this important study.
Sincerely yours,

K4. SITE SPECIFIC LETTER FOR REPORTING ≥ SECOND POSITIVE AUTOANTIBODY RESULTS: GEORGIA/FLORIDA (child's results) **(**used starting in August 2013)

Georgia Regents University
Medical College of Georgia
Center for Biotechnology and Genomic Medicine

TEDDY
Center for Biotechnology and Genomic Medicine
Medical College of Georgia
1120 15th Street, CA-4124
Augusta, GA 30912-2400

Tel: 1-888-225-7785
Tel: 706-721-4161
Fax: 706-721-3688

Date

Address

Dear (Parent Contact Name),

This is a follow-up letter to the telephone call we had about your child's antibody test results. Your child's test results are listed below.

Name of Antibody Test	Normal Level	Your Child's Results	Positive or Negative
IA-2A	≤ 0.03		
GADA	≤ 0.032		
IAA	≤ 0.01		
ZnT8A	< 0.020		

Three of your child's test results were negative or normal. However, one of your child's test results was positive or above the normal level. Your child has tested positive for this antibody more than once.

Among children with your child's genetic test results, we expect _____ (3 for US GP, 14 for US FDR) out of 100 children will develop type 1 diabetes. Because your child has tested positive for this antibody more than once this indicates that your child's risk for type 1 diabetes has increased. This does NOT mean your child will get diabetes for sure. When your child comes in for the next TEDDY study visit, we will test your child's antibodies and blood glucose levels.

If you have any questions or concerns, please call us on our toll free number _____.

Thanks so much for your participation in this important study.

Sincerely yours,

Diane Hopkins, MS, CCRC
TEDDY Study Project Manager

K5. SITE SPECIFIC LETTER FOR REPORTING ≥ SECOND POSITIVE AUTOANTIBODY RESULTS: WASHINGTON (child's results)

PACIFIC NORTHWEST DIABETES RESEARCH INSTITUTE
720 Broadway • Seattle, Washington 98122 • 206-726-1200 • www.pndri.org

<Date>

<Parent of «Fname» «Lname»>
«Address»>
<«City», «State» «Zip»>

Dear _____,

This is a follow-up letter to the telephone call we had about your child's autoantibody test results. Your child's test results are listed below.

Name of Autoantibody Test	Normal Level	Your Child's Results	Positive or Negative
IA-2A	≤ 5		
GADA	≤ 20		
IAA	≤ 0.01		
ZnT8	≤ 0.020		

Three of your child's test results were negative or normal. However, one of your child's test results was positive or above the normal level. Your child has tested positive for this autoantibody more than once.

Among children with your child's genetic test results, we expect <_____ (3 for GP, 14 for FDR)> out of 100 children will develop type 1 diabetes. Because your child has tested positive for this autoantibody more than once this indicates that your child's risk for type 1 diabetes has increased. This does NOT mean your child will get diabetes for sure. When your child comes in for the next TEDDY study visit, we will test your child's autoantibodies and blood glucose levels.

If you have any questions or concerns, please call us on our toll free number 1-888-324-2140.

Thanks so much for your participation in this important study.

Sincerely yours,

Investigator that reported results

K6. SITE SPECIFIC LETTER FOR REPORTING ≥ SECOND POSITIVE AUTOANTIBODY RESULTS: SWEDEN (child's results) (started using September 2014)

En Autoantikropp 140930

Vid två provtagningstillfällen efter varandra har det visat sig att ditt barn har utvecklat en av fyra möjliga autoantikroppar. Det betyder att provresultat för en av dessa autoantikroppar låg över den normala gränsen.

Utifrån detta resultat uppskattar vi att ditt barns risk för att utveckla typ 1 diabetes är 15 %. Med detta menas att av 100 barn med liknande resultat kommer 15 barn att utveckla typ 1 diabetes.

Vi kommer att fortsätta kontrollera ditt barns autoantikroppar och även mäta glukos i blodet (kallas också blodsocker) vid varje TEDDY besök. Vi vill även göra er uppmärksamma på vilka symtom som kan vara tecken på diabetes.

Symtom att lägga märke till är:

- Ökad törst
- Kissar mycket och ofta
- Kissar i sängen efter det att barnet blivit torr på natten
- Viktminskning trots att barnet äter som vanligt
- Ökad trötthet, ingen energi
- Illamående
- Kräkningar
- Återkommande svampinfektioner

Har ni frågor hör gärna av er till er TEDDY sjuksköterska.

Autoantikropp	Referensvärde	Ditt barns resultat	Positiv/Negativ
IA-2A	< 5		
GADA	< 33		
IAA	≤ 0.95		
ZnT8A	≤ 0,020		

L1a. SITE SPECIFIC LETTER FOR REPORTING NEGATIVE AUTOANTIBODY RESULTS WHEN PREVIOUS RESULTS HAVE BEEN POSITIVE: COLORADO (child's results) (used through August 2014)

Barbara Davis Center for Childhood Diabetes
The University of Colorado at Denver and Health Sciences Center
1775 N. Ursula St
Aurora, Colorado 80045

Parent's Name
Address
Address
TEDDY ID

Dear Parents (or person who signed the informed consent),

We are writing to tell you about the autoantibody test results from (CHILD'S NAME)'s TEDDY study visit on (DATE OF LAST CLINIC VISIT) _____. The results of these tests are **negative**.

Autoantibody Test	Your Child's Result	Normal Level	Meaning
IA-2/ICA 512	-0.000	<	negative
GAD65	-0.000	<	negative
IAA	-0.000	<	negative

Your child's baseline genetic risk for developing type 1 diabetes was 3 out of 100 (14 of 100) when you joined the TEDDY Study. At a previous visit, your child had tested positive for one or more of these autoantibodies. Having had a positive test may slightly increase this baseline risk. Autoantibody results often change over time. Even though your child's tests were negative at this visit, autoantibodies can reappear at anytime in childhood. They usually occur 1 to 2 years before the onset of diabetes. A negative test does not reduce your child's risk of diabetes unless all of the tests in the future are negative. We will continue to test your child at each TEDDY visit. As always, all tests are free of charge and your participation in TEDDY is voluntary.

If you have any questions about these test results or the TEDDY study, please call us at 303-315-0115. We will contact you soon about your next appointment, so please be sure let us know if you have a change of address or phone number.

Thank you for taking part in this diabetes study. We look forward to seeing you at your next clinic visit.

Sincerely,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

L1b. SITE SPECIFIC LETTER FOR REPORTING NEGATIVE AUTOANTIBODY RESULTS WHEN PREVIOUS RESULTS HAVE BEEN POSITIVE: COLORADO IN SPANISH (child's results) (used through August 2014)

Barbara Davis Center for Childhood Diabetes
The University of Colorado at Denver and Health Sciences Center
1775 N. Ursula St
Aurora, Colorado 80045

Parent's Name
Address
Address
TEDDY ID

Estimado Padre de Familia (or person who signed the informed consent),

Le estamos escribiendo para informarle sobre los resultados de las prueba de anticuerpos de (CHILD'S NAME) de la visita TEDDY de (DATE OF LAST CLINIC VISIT) _____. Los resultados de estas pruebas son **negativos**.

Pruebas Anticuerpos	Resultado de su hijo/a	Nivel Normal	Significado
IA-2/ICA 512	-0.000	<	negativo
GAD65	-0.000	<	negativo
IAA	-0.000	<	negativo

La base del riesgo genético de desarrollar diabetes tipo 1 es de 3 de cada 100 (14 de 100) cuando se unió al Estudio TEDDY. En una cita previa, su hijo/a dio positivo a uno o mas de estos anticuerpos. El haber tenido una prueba positiva pueda incrementar ligeramente la base de este riesgo. Los resultados de los anticuerpos a veces cambian con el tiempo. A pesar de que los resultados fueron negativos en esta visita. Los anticuerpos pueden volver ha aparecer en cualquier momento durante la niñez. Usualmente ocurren de 1 a 2 años antes del comienzo de la diabetes. Una prueba negativa no reduce el riesgo de diabetes a menos que todas las pruebas en el futuro sean negativas. Continuaremos analizando a su niño/a en cada visita TEDDY. Y como siempre, todas las pruebas son libres de costo y su participación en TEDDY es voluntaria.

Si tiene cualquier pregunta sobre los resultados de estas pruebas o el Estudio TEDDY por favor llámenos al 303-315-0115. Nos contactaremos con usted pronto para su próxima cita, así que, por favor déjenos saber si cambio de dirección o numero de teléfono.

Gracias por formar parte en este estudio de diabetes. Esperamos verlo en su próxima visita a la clínica.

Sinceramente,
Marian J. Rewers, MD, PhD
Investigador Principal, Estudio TEDDY

L2a. SITE SPECIFIC LETTER FOR REPORTING NEGATIVE AUTOANTIBODY RESULTS WHEN PREVIOUS RESULTS HAVE BEEN POSITIVE: COLORADO (child's results) (used beginning August 2014)

To the parents of: 1/26/2010
JANE DOE
100 MAIN STREET 100000
DENVER, CO 80000

Dear Parents,
This is a follow-up letter to the telephone call we had about your child's autoantibody test results. Your child's test results are listed below.

Antibody Test	Your child's result	Normal Level	Meaning
GAD65	0.002	<= 0.032	Negative
IA-2	-0.001	<= 0.03	Negative
IAA	0	<= 0.01	Negative
ZnT8		<0.200	Negative

All of your child's test results were negative or normal. At previous visits your child has tested positive for one of these autoantibodies. Autoantibody test results often change over time.

Among children with your child's genetic test results, we expect _____ (3 for US GP, 14 for US FDR) out of 100 children will develop type 1 diabetes. Because your child has had a positive autoantibody test in the past, your child's risk for type 1 diabetes may be slightly higher than this number.

A negative test result does not reduce your child's risk of diabetes unless future tests are consistently negative. We will continue to test your child at each TEDDY visit. As always, all tests are free of charge and taking part in TEDDY is voluntary.

If you have any questions about these test results or the TEDDY study, please call us at 303-724-7577. We will contact you soon about your next appointment. Please let us know if you have a change of address or phone number.

Thank you for taking part in this important study. We look forward to seeing you at your next clinic visit.

Sincerely,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

L2b. SITE SPECIFIC LETTER FOR REPORTING NEGATIVE AUTOANTIBODY RESULTS WHEN PREVIOUS RESULTS HAVE BEEN POSITIVE: COLORADO IN SPANISH (child's results) (used beginning August 2014)

Estimados Padres,
Esta es una carta de seguimiento a la llamada telefónica que tuvimos con usted acerca de los resultados de la prueba de anticuerpos de su hijo/a. Los resultados de su hijo/a son los siguientes:

Prueba Anticuerpo	Resultados de su hijo/a	Nivel Normal	Significado
GAD65	0.002	<= 0.032	Negativo
IA-2	-0.001	<= 0.03	Negativo
IAA	0	<= 0.01	Negativo
ZnT8		<0.200	Negativo

Todos los resultados de las pruebas de su hijo/a son negativos o normales. En visitas anteriores, su hijo dio positivo para uno de estos autoanticuerpos. Los resultados de las pruebas de autoanticuerpos muchas veces cambian con el tiempo.

Entre los niños que tienen los mismos resultados de pruebas genéticas como su hijo/a, esperamos que _____ (3 para US PG, 14 para US PDPG) de100 niños desarrollaran diabetes tipo 1. Porque su hijo/a resulto positivo para una prueba de autoanticuerpo en el pasado, el riesgo de su hijo/a para desarrollar diabetes tipo 1 puede ser un poco más elevado que este número.

Un resultado de prueba negativo no reduce el riesgo de su hijo/a para la diabetes a menos que pruebas futuras sean consistentemente negativas. Continuaremos haciendo pruebas a su hijo/a en cada visita de TEDDY. Como siempre, todas las pruebas son libres de costo y tomar parte de este estudio es voluntario.

Si tiene alguna pregunta acerca de los resultados de estas pruebas o del estudio TEDDY, por favor llame al 303-724-7577. Pronto nos contactaremos con usted para programar su próxima cita. Por favor déjenos saber si haya algún cambio en su dirección o número telefónico.

Gracias por tomar parte de este importante estudio. Esperamos mirarlos pronto en su siguiente visita.

Sinceramente,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

ABNegPrevPos 8202014

L3. SITE SPECIFIC LETTER FOR REPORTING NEGATIVE AUTOANTIBODY RESULTS WHEN PREVIOUS RESULTS HAVE BEEN POSITIVE: FINLAND (child's results)

Hyvät _____:n vanhemmat,

saitte jo etukäteen puhelimitse tiedon lapsenne vasta-ainetuloksista. Tulokset on lueteltu alla:

Vasta-ainetutkimus	***Normaaliarvo***	**Lapsenne tulos**	**Positiivinen tai negatiivinen**
ICA 512	alle		
GAD	alle		
IAA	alle		

Kaikki lapsenne vasta-ainetulokset olivat negatiivisia eli normaaleja. Aikaisemmilla TEDDY-käynneillä lapseltanne on löytynyt jotakin näistä vasta-aineista. Vasta-ainetulokset usein vaihtelevat ajan kuluessa.

Jos ajatellaan sellaisia lapsia, joilla on samanlainen peritty diabetesalttius kuin Teidän lapsellanne, noin 7 lasta sadasta sairastuu joskus tyypin 1 diabetekseen. Koska Teidän lapsellanne on aikaisemmin löytynyt diabetekseen liittyviä vasta-aineita, hänen riskinsä sairastua diabetekseen saattaa olla hieman tätä suurempi. Negatiivinen vasta-ainetulos ei vähennä lapsenne sairastumisriskiä, elleivät tulokset säily jatkossa pysyvästi nega-tiivisina.

Kun lapsenne tulee seuraavalle TEDDY-käynnille, tutkimme hänen vasta-ainetasonsa uudelleen ja tiedotamme teille tuloksista. Jos teillä on jotakin kysyttävää tai haluatte muuten keskustella asioista, soittaakaa meille puh._____.

Tervetuloa seuraavalle TEDDY-käynnillenne _____.

Lämpimät kiitoksemme siitä, että osallistutte tähän tärkeään tutkimukseen.

Kunnioittaen

Professori Olli Simell
TYKS Lastenklinikka

L4. SITE SPECIFIC LETTER FOR REPORTING NEGATIVE AUTOANTIBODY RESULTS WHEN PREVIOUS RESULTS HAVE BEEN POSITIVE: GERMANY (child's results)
Brief: negatives AK-Ergebnis nach vorherigem positiven AK

Familie

München, ...

Sehr geehrte Familie .....,

die Antikörperuntersuchung vom ..... bei Ihrem Kind ..... (geb. .....) ergab folgende Werte:

Antikörpertest	**Normalbereich**	**Antikörperergebnis Ihres Kindes**	**Positiv oder Negativ**
Antiköper IA2	≤ 9 WHO units/ml		
Glutamatdecarboxylase-AK (GADA)	≤ 20 WHO units/ml		
Insulinautoantikörper (Microassay)	≤ 0,95		

Wie bereits telefonisch besprochen, sind alle drei Antikörpertests jetzt negativ, d.h. normal, ausgefallen. Bei der letzten Blutuntersuchung wurde Ihr Kind für einen Antikörper positiv getestet. Antikörpertestergebnisse können sich im Laufe der Zeit verändern.

Bei Kindern mit genetischen Anlagen entwickeln 14 (bzw 3) von 100 Kindern einen Typ 1 Diabetes. Da Ihr Kind in der Vergangenheit für einen Antikörper positiv getestet wurde, besteht ein leicht erhöhtes Risiko für Ihr Kind an Diabetes zu erkranken.

Ein negatives Testergebnis bedeutet keine Reduzierung des Diabetesrisikos bis nicht alle weiteren Tests negativ ausfallen.
Wenn Ihr Kind zur nächsten Blutentnahme geht, werden wir wieder die Antikörper untersuchen und Ihnen das Ergebnis mitteilen.

Falls Sie Fragen haben, können Sie uns unter der gebührenfreien Telefonnummer 0800 / 33 8 333 9 kontaktieren.

Vielen Dank für Ihre Teilnahme an der TEDDY Studie!

Mit freundlichen Grüßen,

Prof. Dr. Anette-G. Ziegler Dr. med. Peter Achenbach

L5. SITE SPECIFIC LETTER FOR REPORTING NEGATIVE AUTOANTIBODY RESULTS WHEN PREVIOUS RESULTS HAVE BEEN POSITIVE: GEORGIA/FLORIDA (child's results) (used through September 2014)

GRU
GEORGIA REGENTS UNIVERSITY
AUGUSTA

Georgia Regents University
Medical College of Georgia
Center for Biotechnology and Genomic Medicine

TEDDY
Center for Biotechnology and Genomic Medicine
Medical College of Georgia
1120 15th Street, CA-4124
Augusta, GA 30912-2400

Tel: 1-888-225-7785
Tel: 706-721-4161
Fax: 706-721-3688

Date

Address

Dear _____,

This is a follow-up letter to the telephone call we had about your child's antibody test results. Your child's test results are listed below.

Name of Antibody Test	Normal Level	Your Child's Results	Positive or Negative
IA-2A	≤ 0.03		
GADA	≤ 0.032		
IAA	≤ 0.01		
ZnT8A	≤ 0.020		

All of your child's test results were negative or normal. At previous visits your child has tested positive for one of these antibodies. Antibody test results often change over time.

Among children with your child's genetic test results, we expect _____ (3 for US GP, 14 for US FDR) out of 100 children will develop type 1 diabetes. Because your child has had a positive antibody test in the past, your child's risk for type 1 diabetes may be slightly higher than this number. A negative test result does not reduce your child's risk of diabetes unless future tests are consistently negative.

When your child comes in for the next TEDDY study visit, we will test your child's antibodies again and let you know the results.

If you have any questions or concerns, please call us on our toll free number _____.

Thanks so much for your participation in this important study.

Sincerely,

Diane Hopkins, MS, CCRC
TEDDY Study Project Manager

L6. SITE SPECIFIC LETTER FOR REPORTING NEGATIVE AUTOANTIBODY RESULTS WHEN PREVIOUS RESULTS HAVE BEEN POSITIVE: GEORGIA/FLORIDA (child's results) (used starting September 2014)

Georgia Regents University
Medical College of Georgia
Center for Biotechnology and Genomic Medicine

TEDDY
Center for Biotechnology and Genomic Medicine
Georgia Regents University
1120 15th Street, CA-4124
Augusta, GA 30912-2400

Tel: 1-888-225-7785
Tel: 706-721-4161
Fax: 706-721-3688

Date

Address

Dear _____,

This is a follow-up letter to the telephone call we had about your child's autoantibody test results. Your child's test results are listed below.

Name of Autoantibody Test	Normal Level	Your Child's Results	Positive or Negative
IA-2A	≤ 0.03		
GADA	≤ 0.032		
IAA	≤ 0.01		
ZnT8A	≤ 0.020		

All of your child's test results were negative or normal. At previous visits, your child has tested positive for one of these autoantibodies. Autoantibody test results often change over time.

Among children with your child's genetic test results, we expect _____ (3 for US GP, 14 for US FDR) out of 100 children will develop type 1 diabetes. Because your child has had a positive autoantibody test in the past, your child's risk for type 1 diabetes may be slightly higher than this number. A negative test result does not reduce your child's risk of diabetes unless future tests are consistently negative.

When your child comes in for the next TEDDY study visit, we will test your child's autoantibodies again and let you know the results.

If you have any questions or concerns, please call us on our toll free number _____.

Thanks so much for your participation in this important study.

Sincerely,

Diane Hopkins, MS, CCRC
TEDDY Study Project Manager

Version Date: 9/15/2014

L7. SITE SPECIFIC LETTER FOR REPORTING NEGATIVE AUTOANTIBODY RESULTS WHEN PREVIOUS RESULTS HAVE BEEN POSITIVE: WASHINGTON (child's results)

PACIFIC NORTHWEST DIABETES RESEARCH INSTITUTE
720 Broadway • Seattle, Washington 98122 • 206-726-1200 • www.pndri.org

Date

Parent of «Fname» «Lname»
«Address»
«City», «State» «Zip»

Dear _____,

This is a follow-up letter to the telephone call we had about **child's name's** autoantibody test results. Your child's test results are listed below.

Name of Autoantibody Test	Normal Level (US Sites)	Your Child's Results	Positive or Negative
IA-2A	≤ 5		
GADA	≤ 20		
IAA	≤ 0.01		
ZnT8	≤ 0.020		

All of **child's name's** test results were negative or normal. At prior visits your child has tested positive for one of these autoantibodies. Autoantibody test results often change over time.

Among children with your child's genetic test results, we expect _____ **(3 for US GP, 14 for US FDR)** out of 100 children will develop type 1 diabetes. Because your child has had a positive autoantibody test in the past, your child's risk for type 1 diabetes may be slightly higher than this number. A negative test result does not reduce your child's risk of diabetes unless future tests are consistently negative.

When your child comes in for the next TEDDY study visit, we will test your child's autoantibodies again and let you know the results.

If you have any questions or concerns, please call us on our toll free number 1-888-324-2140.

Thanks so much for taking part in this important study.

Sincerely yours,

Investigator who reported results

M. MODEL LETTER FOR REPORTING NEGATIVE AUTOANTIBODY RESULTS IN CASES WITH A PREVIOUS SINGLE AUTOANTIBODY POSITIVE TEST RESULT (child's results) – ADDED TO MOO - MAY 2017

Parent Doe
123 Main Street
Anytown, WA 98123

Dear _____,

This is a follow-up letter to the telephone call we had about your child's autoantibody test results. Your child's test results are listed below.

Name of Autoantibody Test	Normal Level – TEDDY Assay (US Sites)	Normal Level – TEDDY Assay (European Sites)	Normal Level– Harmonized Assay (US Sites)	Normal Level– Harmonized Assay (European Sites)	Your Child's Results	Positive or Negative
IA-2A	≤ 0.03 [index] – NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤ 9 WHO units/ml - NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤5	<5		
GADA	≤ 0.032 [index] - – NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤ 20 WHO units/ml - – NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤20	<33		
IAA	≤ 0.01 [index]	≤ 0.95 [index]	No harmonized assay; TEDDY assay will continue to be used	No harmonized assay; TEDDY assay will continue to be used		
ZnT8A	≤ 0.020					

All of your child's test results were negative or normal. At previous visits your child has tested positive for one of these autoantibodies. Autoantibody test results often change over time.

Among children with your child's genetic test results, we expect _____ (3 for US GP, 14 for US FDR, European sites to specify their risk by country) out of 100 children will develop type 1 diabetes. Because your child has had a positive autoantibody test in the past, your child's risk for type 1 diabetes may be slightly higher than this number.

When your child comes in for the next TEDDY study visit, we will test your child's autoantibodies again and let you know the results.

If you have any questions or concerns, please call us on our toll free number _____.

Your next TEDDY study visit is scheduled for _____(provide data and time). We look forward to seeing you then.

Thanks so much for your participation in this important study.

Sincerely yours,

Site PI

GRADE LEVEL: 8.3

N. MODEL TELEPHONE SCRIPT FOR REPORTING MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS (child's results) – EDITS MADE TO MODEL LETTER – MAY 2017

Note: the following model letter presumes the parent has received previous letters indicating one or more positive test results; if not, additional explanation of autoantibody testing is warranted.

Hello, my name is _____ and I am calling from the TEDDY Study. May I speak with _____ (parent/legal guardian of TEDDY child)? Do you have a few minutes to talk?"

[If yes, continue]

[If no, record when to re-call and then say goodbye.]

I am calling with your child's autoantibody test results from the last TEDDY study visit. _____ (number of positive tests) of your child's autoantibody tests came back positive, or above normal. _____ (number of negative tests) of your child's autoantibody tests came back negative or normal:

Name of Autoantibody Test	Normal Level – TEDDY Assay (US Sites)	Normal Level – TEDDY Assay (European Sites)	Normal Level– Harmonized Assay (US Sites)	Normal Level– Harmonized Assay (European Sites)	Your Child's Results	Positive or Negative
IA-2A	≤ 0.03 [index] – NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤ 9 WHO units/ml - NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤5	<5		
GADA	≤ 0.032 [index] - – NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤ 20 WHO units/ml - – NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤20	<33		
IAA	≤ 0.01 [index]	≤ 0.95 [index]	No harmonized assay; TEDDY assay will continue to be used	No harmonized assay; TEDDY assay will continue to be used		
ZnT8A	≤ 0.020					

Because your child has tested positive for multiple autoantibodies more than once, we believe your child's risk for type 1 diabetes has significantly increased. (Although we have previously told you that your child is at increased risk for type 1 diabetes)* Current scientific studies indicate that 70 out of 100 children with autoantibody testing results like your child's, will go on to develop type 1 diabetes in the next 10 years of your child's life. (This risk is based on new scientific studies and is greater than the risk level we have told you in the past.)*

Scientific studies also show that when a child's type 1 diabetes is diagnosed early, the child receives treatment right away. Often, these children do not need to be hospitalized at the time of diagnosis. So, we will be carefully checking your child's blood glucose and hemoglobin A1c levels for diabetes at each TEDDY study visit. Every 6 months we will do a special test called an oral glucose tolerance test. We will give you more information about the test before it is scheduled.

Between TEDDY visits, it is a good idea to watch your child carefully for any signs of type 1 diabetes. Look for weight loss even though your child is eating a lot. Notice if your child is very thirsty or peeing a lot. Sometimes children who have been dry at night begin to wet the bed. Other children may be sick to their stomach, have blurry vision, frequent yeast infections or act very tired. Take your child to the doctor if any of these symptoms last more than a few days. We can send you more information about diabetes or you can find this information on our TEDDY website www.teddystudy.org.

We recommend that you share your child's test results with your child's doctor. We can give you a letter to take to your doctor explaining these results. Feel free to give the doctor our toll free number. We will be glad to discuss your child's test results with your doctor.

Do you have any questions or concerns that I can answer now? **[If parents seem overly concerned, go over the numbers again, and address any concerns. If needed, offer to put them in contact with PI or counselor.]**

We will be sending you a letter describing your child's autoantibody test results. If you have any questions or concerns, please call our toll free number _____.

Your next TEDDY study visit is scheduled for _____(provide data and time). We look forward to seeing you then.

*suggested wording for families who have previously been told 50 out of 100

GRADE LEVEL: 8.2

O. MODEL LETTER FOR REPORTING MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS (child's results) **– EDITS MADE TO MODEL LETTER – MAY 2017**

Date

Address

Dear (Parent Contact Name),

This is a follow-up letter to the telephone call we had about your child's autoantibody test results. Your child's test results are listed below.

Name of Autoantibody Test	Normal Level – TEDDY Assay (US Sites)	Normal Level – TEDDY Assay (European Sites)	Normal Level– Harmonized Assay (US Sites)	Normal Level– Harmonized Assay (European Sites)	Your Child's Results	Positive or Negative
IA-2A	≤ 0.03 [index] – NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤ 9 WHO units/ml - NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤5	<5		
GADA	≤ 0.032 [index] - – NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤ 20 WHO units/ml - – NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤20	<33		
IAA	≤ 0.01 [index]	≤ 0.95 [index]	No harmonized assay; TEDDY assay will continue to be used	No harmonized assay; TEDDY assay will continue to be used		
ZnT8A	≤ 0.020					

Your child has tested positive for multiple autoantibodies more than once. This means that your child's risk for getting type 1 diabetes is significantly increased. There are now many scientific studies that have followed children who have multiple autoantibodies. These studies tell us that your child's risk of getting diabetes in the next 10 years is greater than 70%. This means that out of 100 children with test results like your child's, 70 or more will develop type 1 diabetes in the next 10 years.

We know that when a child's type 1 diabetes is diagnosed early, the child receives treatment right away. Often, these children do not need to be hospitalized at the time of diagnosis. So, we will be checking your child's autoantibodies, blood glucose and hemoglobin A1c levels at each TEDDY study visit. We will

also do a special test – called an oral glucose tolerance test- every 6 months to check your child for type 1 diabetes.

We want you to watch your child carefully for any signs of type 1 diabetes. Things to look for include:

- ✓ Weight loss even though your child is eating a lot
- ✓ Increased thirst
- ✓ Peeing a lot
- ✓ Wetting the bed in a child who was previously dry
- ✓ Nausea
- ✓ Vomiting
- ✓ Frequent yeast infections
- ✓ No energy, feeling tired

We think it is a good idea to talk to your child's doctor about this. We can give you a letter to take to your doctor explaining these results. Feel free to give the doctor our toll free number. We will be glad to discuss your child's test results with your child's doctor, with your signed permission.

If you have any questions or concerns, please call us on our toll free number _____.

Sincerely,

GRADE LEVEL 7.9

P1a. SITE SPECIFIC LETTER FOR REPORTING MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: COLORADO (child's results) (used through August 2014)

Barbara Davis Center for Childhood Diabetes
The University of Colorado at Denver and Health Sciences Center
1775 N. Ursula St
Aurora, Colorado 80045

Parent's Name
Address
Address
TEDDY ID

Dear Parents,
Thank you for taking the time to speak with us about (CHILD'S NAME) autoantibody test results. As we talked about on the phone, your child's autoantibody test results from the (DATE OF LAST CLINIC VISIT) visit are listed below.

Autoantibody Test	Your Child's Result		Normal Level	Meaning
IA-2/ICA 512	+0.000	<		positive
GAD65	-0.000	<		negative
IAA	-0.000	<		positive

Your child's test results were positive or above normal for several autoantibodies. Because your child has tested positive for several autoantibodies more than once, we believe your child's risk for type 1 diabetes has significantly increased. Your child's baseline genetic risk for developing type 1 diabetes was 3 out of 100 (14 of 100) when you joined the TEDDY Study. Among children with these autoantibody test results, we expect 50 out of 100 children will develop type 1 diabetes.

We will continue to test your child's autoantibodies and blood glucose level at each TEDDY visit. As always, all tests are free of charge and taking part in TEDDY is voluntary. In the meant time, it is a good idea to watch your child carefully for any signs of type 1 diabetes. Things to look for include:

- ✓ **Increased thirst**
- ✓ **Urinating a lot**
- ✓ Weight loss even though your child is eating a lot
- ✓ Wetting the bed in a child who was previously not
- ✓ Nausea
- ✓ Vomiting
- ✓ Frequent yeast infections
- ✓ No energy, feeling tired

We recommend that you take your child to the doctor or call the TEDDY clinic if these symptoms last more than a few days. You may like to share your child's test results with your doctor. We can give you a letter to take to your doctor explaining these results. If you would like us to discuss these results with your doctor, feel free to have the doctor contact us at 303.315.0115.

We will contact you soon about your next appointment, so please let us know if you have a change in address or phone number. Thank you for taking part in this study. We look forward to seeing you at your next visit.

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

P1b. SITE SPECIFIC LETTER FOR REPORTING MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: COLORADO IN SPANISH (child's results) (used through August 2014)

Barbara Davis Center for Childhood Diabetes
The University of Colorado at Denver and Health Sciences Center
1775 N. Ursula St
Aurora, Colorado 80045

Parent's Name
Address
Address
TEDDY ID

Estimado Padre de Familia,
Gracias por tomarse el tiempo para hablar con nosotros sobre los resultados de la prueba de anticuerpos de (CHILD'S NAME). Como ya lo hablamos con usted por teléfono, los resultados de la prueba de anticuerpo de su hijo/a de la visita de (DATE OF LAST CLINIC VISIT) se listan a continuación.

Prueba de Anticuerpos	Los Resultados de su hijo/a	Nivel Normal	Significado
IA-2/ICA 512	+0.000	<	positivo
GAD65	-0.000	<	negativo
IAA	-0.000	<	positivo

Los resultados de la prueba de su hijo/a son positivos o están sobre lo normal para varios anticuerpos. Porque su hijo/a ha salido positivo para varios anticuerpos más de una vez, creemos que el riesgo de diabetes tipo 1 ha incrementado significativamente. La base del riesgo genético de su hijo/a para desarrollar diabetes tipo1 era de 3 de cada 100 (14 de 100) cuando se unió al Estudio TEDDY. Entre los niños con estos resultados de la prueba de anticuerpos, esperamos que 50 de cada 100 desarrollaran diabetes tipo 1.

Continuaremos haciendo pruebas de anticuerpos y niveles de glucosa en la sangre a su hijo/a en cada visita de TEDDY. Como siempre todas las pruebas son libres de costo y formar parte de TEDDY es voluntario. Mientras tanto, es buena idea observar a su hijo/a cuidadosamente por cualquier señal de diabetes tipo 1. Cosas que hay que buscar incluye:

- ✓ **Incremento de sed**
- ✓ **Orinar demasiado**
- ✓ Perdida de peso a pesar que su hijo/a esta comiendo mucho
- ✓ Mojar la cama cuando previamente no lo hacia
- ✓ Nauseas
- ✓ Vomito
- ✓ Frecuentes infecciones causada por Candidiasis
- ✓ Sin energía, sentirse cansado/a

Recomendamos que lleve a su hijo/a al medico o llame a la clínica TEDDY si estos síntomas duran por varios días. Quizás desee compartir los resultados con su medico. Podemos darle una carta para su medico

explicando estos resultados. Si usted desea podemos discutir estos resultados con su medico, siéntase con la libertad de que su medico nos contacte al 303.315.0115.

Pronto lo/la contactaremos para su próxima cita, así que, por favor déjenos saber si ha cambiado de dirección o numero de teléfono. Esperamos verlo/a en su próxima visita.

Marian J. Rewers, MD, PhD
Investigador Principal, Estudio TEDDY

P2a. SITE SPECIFIC LETTER FOR REPORTING MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: COLORADO (child's results) (used August 2014 – September 2017)

Dear Parents,
This is a follow-up letter to the telephone call we had about your child's autoantibody test results. Your child's test results are listed below.

Antibody Test	Your child's result	Normal Level	Meaning
GAD65	0.038	<= 0.032	Positive
IA-2	-0.001	<= 0.03	Negative
IAA	0.029	<= 0.01	Positive
Znt8			Postive

Your child has tested positive for multiple autoantibodies more than once. This means your child's risk for getting type 1 diabetes is significantly increased. Based on these results, we estimate your child's risk of getting diabetes to be greater than 50%. This means out of 100 children, it is likely that 50 or more will go on to develop type 1 diabetes.

We will be checking your child's autoantibodies and blood glucose levels at each TEDDY study visit. In the meantime, it is a good idea to watch your child carefully for any signs of type 1 diabetes. Things to look for include:

- ✓ Weight loss even though your child is eating a lot
- ✓ Increased thirst
- ✓ Peeing a lot
- ✓ Wetting the bed in a child who was previously dry
- ✓ Nausea
- ✓ Vomiting
- ✓ Frequent yeast infections
- ✓ No energy, feeling tired

You may like to share your child's test results with your child's doctor. We can give you a letter to take to your doctor explaining these results. If you have any questions about these test results or the TEDDY study, please call us at 303-724-7577. We will contact you soon about your next appointment. Please be sure to let us know if you have a change of address or phone number.

Thank you for taking part in this important study. We look forward to seeing you at your next clinic visit.

Sincerely,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

P2b. SITE SPECIFIC LETTER FOR REPORTING MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: COLORADO IN SPANISH (child's results) (used August 2014 – September 2017)

Estimados padres,
Esta es una carta de seguimiento a la llamada que tuvimos con usted acerca de los resultados de autoanticuerpos de su hijo/a. Los resultados de su hijo/a son los siguientes:

Prueba Anticuerpo	Resultados de su hijo/a	Nivel Normal	Significado
GAD65	0.038	<= 0.032	Positivo
IA-2	-0.001	<= 0.03	Negativo
IAA	0.029	<= 0.01	Positivo
Znt8			Positivo

Los resultados de su hijo/a han sido positivos para múltiples autoanticuerpos más de una vez. Esto significa que el riesgo de su hijo/a para desarrollar la diabetes tipo 1 ha incrementado significativamente. Basado en estos resultados, estimamos que el riesgo de su hijo/a para desarrollar la diabetes es más de 50%. Esto significa que de 100 niños, es posible que 50 o más desarrollen la diabetes tipo 1. Estaremos monitoreando los autoanticuerpos y el nivel de azúcar en la sangre de su hijo/a en cada visita de TEDDY. Mientras tanto, es una buena idea observar cuidadosamente a su hijo/a para cualquier síntoma de la diabetes tipo 1. Cosas que hay que buscar incluyen:

- ✓ Pérdida de peso a pesar que su hijo/a esta comiendo mucho
- ✓ Incremento de sed
- ✓ Orinar demasiado
- ✓ Mojar la cama cuando previamente no lo hacia
- ✓ Nausea
- ✓ Vómitos
- ✓ Infecciones frecuentes causadas por Candidiasis
- ✓ Falta de energía, sentirse cansado/a

Quizás desee compartir los resultados de su hijo/a con su médico. Nosotros podemos proveerle una carta para llevar al médico explicando estos resultados. Si usted tiene alguna pregunta acerca de estos resultados o acerca del estudio TEDDY, por favor llame al 303-724-7577. Nos contactaremos pronto con usted para programar su próxima cita. Por favor déjenos saber si usted tiene algún cambio de dirección o número telefónico.

Gracias por tomar parte de este importante estudio. Esperamos mirarlos pronto en su siguiente cita.

Sinceramente,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

AB+MultiPers8202014

P3. SITE SPECIFIC LETTER FOR REPORTING MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: COLORADO (child's results) (used starting September 2017)

Dear Parents,
The results of the TEDDY autoantibody tests for drawn on are as follows:

Antibody Test	Your child's result	Normal Level	Meaning
GAD65		≤ 20	
IA-2		≤ 5	
IAA		≤ 0.01	
Znt8		≤ 0.02	

Your child has tested positive for multiple autoantibodies more than once. This means your child's risk for getting type 1 diabetes is significantly increased. Current scientific studies show that out of 100 children with multiple autoantibodies, 70 will go on to develop type 1 diabetes within 10 years.

We will be checking your child's autoantibodies and blood glucose levels at each TEDDY study visit. We also recommend doing an oral glucose tolerance test every 6 months. We will carefully monitor your child for the development of diabetes. Catching it early can prevent some children from becoming very sick. In the meantime, it is a good idea to watch your child carefully for any signs of type 1 diabetes. Things to look for include:

Increased thirst	Weight loss even though your child is eating a lot
Peeing a lot	Wetting the bed in a child who was previously not
Nausea	Frequent yeast infections
Vomiting	No energy, feeling tired

You may like to share these test results with your child's doctor. We can give you a letter to give to your doctor that explain these results. If you have any questions about these test results or the TEDDY study, please call us at 303-724-7577. We will contact you soon about your next appointment. Please be sure to let us know if you have a change of address or phone number.

Thank you for taking part in this important study. We look forward to seeing you at your next clinic visit.

Sincerely,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

P4. SITE SPECIFIC LETTER FOR REPORTING MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: FINLAND (child's results)

Hyvät _____:n vanhemmat,

saitte jo etukäteen puhelimitse tiedon lapsenne vasta-ainetuloksista. Tulokset on lueteltu alla:

Vasta-ainetutkimus	***Normaaliarvo***	**Lapsenne tulos**	**Positiivinen tai negatiivinen**
ICA 512	alle		
GAD	alle		
IAA	alle		

Kuten näette, **lapsenne vasta-ainetulokset olivat nyt positiivisia eli normaalia korkeampia useamman vasta-aineen osalta.** Koska lapsellanne on nyt toistuvasti ollut positiivisia tuloksia useammasta vasta-aineesta, hänen riskinsä sairastua tyypin 1 diabetekseen on merkittävästi suurentunut. Jos ajatellaan sellaisia lapsia, joilla on samanlaiset vasta-ainetulokset kuin Teidän lapsellanne, noin 50 lasta sadasta sairastuu joskus tyypin 1 diabetekseen.

Tutkimme lapsenne verensokeritason jokaisella TEDDY-käynnillä. Lisäksi on hyvä tarkkailla, ilmaantuuko lapselle jotakin diabetekseen viittaavia oireita.

Diabetekseen viittaavia oireita ovat:
- *laihtuminen, vaikka lapsi syö paljon*
- *lisääntynyt jano*
- *lisääntynyt virtsaaminen*
- *yökastelu aikaisemmin kuivaksi oppineella lapsella*
- *pahoinvointi*
- *oksentelu*
- *toistuvat hiivatulehdukset*
- *väsymys*

Jos lapsellanne on tällaisia oireita pitempään kuin muutaman päivän ajan, suosittelemme, että käytte hänen kanssaan lääkärissä.

Voimme lähettää teille lisää tietoa diabeteksesta, ja löydätte lisää tietoja myös TEDDY-kotisivulta. Jos haluatte keskustella lapsenne tutkimustuloksista myös hänen oman lääkärinsä tai terveydenhoitajansa kanssa, voimme antaa teille tätä varten kirjeen, jossa tutkimustulokset on selitetty. Oma lääkärinne tai terveydenhoitajanne voi myös soittaa meille ja keskustella tuloksista tarvittaessa.

Jos teillä on jotakin kysyttävää tai haluatte muuten keskustella asioista, soittakaa meille puh._____.

Tervetuloa seuraavalle TEDDY-käynnillenne _____.

Lämpimät kiitoksemme siitä, että osallistutte tähän tärkeään tutkimukseen.

Kunnioittaen

Professori Olli Simell
TYKS Lastenklinikka

P5. SITE SPECIFIC LETTER FOR REPORTING MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: GERMANY (child's results) (used through August 2014)

Brief: Bestätigung mehrer positiver AK

Familie

München, 26.01.24

Sehr geehrte Familie .....,

die Antikörperuntersuchung vom ..... bei Ihrem Kind ..... (geb. .....) ergab folgende Werte:

Antikörpertest	**Normalbereich**	**Antikörperergebnis Ihres Kindes**	**Positiv oder Negativ**
Antiköper IA2	≤ 9 WHO units/ml		
Glutamatdecarboxylase-AK (GADA)	≤ 20 WHO units/ml		
Insulinautoantikörper (Microassay)	≤ 0,95		

Wie bereits telefonisch besprochen, waren zwei oder mehrere Antikörpertests positiv, d.h. über dem Normalbereich. Da Ihr Kind bereits mehr als einmal für mehrere Antikörper positiv getestet wurde, gehen wir davon aus, dass ein stark erhöhtes Risiko für Ihr Kind besteht an Typ 1 Diabetes zu erkranken.
Bei Kindern mit genetischen Vererbungsmerkmalen und mehreren positiven Autoantikörpern werden ca. 50 von 100 Kindern Typ 1 Diabetes entwickeln. Vorsichtshalber empfehlen wir, durch Ihren Kinder- oder Hausarzt einen oralen Glucostoleranztest bei Ihrem Kind durchführen zu lassen. Zum jetzigen Zeitpunkt halten wir es außerdem für eine gute Idee, Ihr Kind auf Anzeichen für einen Typ 1 Diabetes zu beobachten:

- Gewichtsverlust
- verstärktes Durstgefühl
- häufiges Wasserlassen
- Bettnässen, obwohl Kind bereits trocken war
- Übelkeit, Erbrechen
- häufige Infektionen
- Müdigkeit, Energielosigkeit

Falls Sie einige dieser Anzeichen über mehrere Tage beobachten können, möchten wir Sie bitten Ihren Kinder- oder Hausarzt aufzusuchen. Wenn Sie wünschen können wir Ihnen jederzeit mehr Informationen über Typ 1 Diabetes zuschicken.

Vielleicht möchten Sie dieses Ergebnis Ihrem Kinder- oder Hausarzt mitteilen. Wir können Ihnen gerne für Ihren Arzt einen Brief mit den Ergebnissen und dessen Bedeutung zukommen lassen. Außerdem möchten wir Sie im Interesse Ihres Kindes darauf hinweisen, diesen Befund streng vertraulich zu behandeln und nicht an Dritte weiterzuleiten. Besonders sollten Sie darauf achten, dass der Befund NICHT in der Krankenakte Ihres Kindes bei Ihrem Kinderarzt abgelegt wird, damit Versicherungen keinen Zugang zu dieser Information erhalten. Sie können Ihrem Kinder- oder Hausarzt auch gerne unsere gebührenfreie Telefonnummer mitteilen und wir werden die Antikörpertestergebnisse mit Ihm besprechen.

Falls Sie Fragen haben, können Sie uns unter der gebührenfreien Telefonnummer 0800 / 33 8 333 9 kontaktieren.

Vielen Dank für Ihre Teilnahme an der TEDDY Studie!

Mit freundlichen Grüßen,

Prof. Dr. Anette-G. Ziegler Dr. med. Peter Achenbach

P6. SITE SPECIFIC LETTER FOR REPORTING MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: GERMANY (child's results) (used August 2014 – August 2017)

HelmholtzZentrum münchen
Deutsches Forschungszentrum für Gesundheit und Umwelt

Klinikum rechts der Isar

Technische Universität München

Lehrstuhl für Diabetes und Gestationsdiabetes

Institut für Diabetesforschung · Ingolstädter Landstraße 1 · 85764 Neuherberg

Univ.- Prof. Dr. med. Anette-Gabriele Ziegler
Direktorin
Institut für Diabetesforschung
Helmholtz Zentrum München

und

Forschergruppe Diabetes
Klinikum rechts der Isar
Technische Universität München

Lehrstuhl für Diabetes und Gestationsdiabetes

und

Forschergruppe Diabetes e. V.
am Helmholtz Zentrum München

Vorname Nachname
Position

Tel. +49(0)89-3187-xxxx
Fax +49(0)89-3187-3144
vorname.nachname@helmholtz-muenchen.de

München, 25.11.2014

Sehr geehrte Familie,

vielen Dank für die Zusendung der Blutprobe.

Die Antikörperuntersuchung vom (Datum) bei xxx ergab folgendes Ergebnis:

Diabetesantikörper:				
IAA:	positiv	Titer:	2,21	units (normal <0,95 units)
GADA:	positiv	Titer:	36,55	WHO units/ml (normal <33 WHO units)
IA2A:	positiv	Titer:	336,69	WHO units/ml (normal <5 WHO units)
ZnT8A:	folgt			

Die Diabetes-Autoantikörper bei xxx sind im Vergleich zu November 2013 stabil/ angestiegen. Da alle Antikörper positiv sind, besteht ein frühes Stadium eines Typ 1 Diabetes.

Das Risiko für erhöhte Blutzuckerwerte und eine notwendige Insulintherapie liegt bei etwa 50% innerhalb von 6 Jahren; das bedeutet, dass 50 von 100 Kindern mit mehreren Diabetes-Autoantikörpern innerhalb von 6 Jahren erhöhte Blutzuckerwerte entwickeln und mit der Insulintherapie beginnen müssen.

Wir empfehlen Ihnen vorsichtshalber weiterhin gelegentlich selbst Blutzuckermessungen (nüchtern und nach dem Frühstück) vorzunehmen und auf mögliche, typische Symptome zu achten:

- ungewöhnlicher Gewichtsverlust
- vermehrter Durst
- häufiges Wasserlassen
- Einnässen

1 von 2

Helmholtz Zentrum München
Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH)
Ingolstädter Landstr. 1
85764 Neuherberg
Telefon +49(0)89 3187 (0)
Telefax +49(0)89 3187 3322

info@helmholtz-muenchen.de
www.helmholtz-muenchen.de

Aufsichtsratsvorsitzende:
MinDir'in Bärbel Brumme-Bothe

Geschäftsführer:
Prof. Dr. Günther Wess
Dr. Nikolaus Blum
Dr. Alfons Enhsen

Registergericht:
Amtsgericht München HRB 6466
USt-IdNr- DE 129521671

Bankverbindung:
Münchner Bank eG
Konto-Nr. 2 158 620
BLZ 701 900 00
IBAN DE04701900000002158620
BIC GENODEF1M01

- Übelkeit, Erbrechen
- Kraftlosigkeit, Müdigkeit
- häufige Pilzinfektionen

Die Bestimmung des zusätzlichen Antikörpers ZnT8 ist wieder etwas verzögert. Wenn diese Werte vorliegen, melden wir uns noch einmal.

Mit Hilfe der nächsten Untersuchung im Rahmen von TEDDY in ca. drei Monaten werden wir den Verlauf der Antikörper weiterhin gerne beobachten.

Wenn Sie Fragen zum Testergebnis oder zur TEDDY-Studie haben, stehen wir gerne zur Verfügung.

Vielen Dank für Ihre tolle Mitarbeit an der TEDDY-Studie.

Mit freundlichen Grüßen,

Ihre

Prof. Dr. med. Anette-G. Ziegler Joanna Stock

Univ.- Prof. Dr. med. Anette-Gabriele Ziegler
Direktorin
Institut für Diabetesforschung
Helmholtz Zentrum München

und

Forschergruppe Diabetes
Klinikum rechts der Isar
Technische Universität München

Lehrstuhl für Diabetes und Gestationsdiabetes

und

Forschergruppe Diabetes e. V.
am Helmholtz Zentrum München

Vorname Nachname
Position

Tel. +49(0)89-3187-xxxx
Fax +49(0)89-3187-3144
vorname.nachname@helmholtz-muenchen.de

Helmholtz Zentrum München
Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH)
Ingolstädter Landstr. 1
85764 Neuherberg
Telefon +49(0)89 3187 (0)
Telefax +49(0)89 3187 3322

info@helmholtz-muenchen.de
www.helmholtz-muenchen.de

Aufsichtsratsvorsitzende:
MinDir'in Bärbel Brumme-Bothe

Geschäftsführer:
Prof. Dr. Günther Wess
Dr. Nikolaus Blum
Dr. Alfons Enhsen

Registergericht:
Amtsgericht München HRB 6466
USt-IdNr- DE 129521671

Bankverbindung:
Münchner Bank eG
Konto-Nr. 2 158 620
BLZ 701 900 00
IBAN DE04701900000002158620
BIC GENODEF1M01

P7. SITE SPECIFIC LETTER FOR REPORTING MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: GERMANY (child's results) (used starting August 2017)

HelmholtzZentrum münchen
Deutsches Forschungszentrum für Gesundheit und Umwelt

Klinikum rechts der Isar

Technische Universität München

Lehrstuhl für Diabetes und Gestationsdiabetes

Institut für Diabetesforschung · Heidemannstr. 1 · 80939 München

Univ.- Prof. Dr. med. Anette-Gabriele Ziegler
Direktorin
Institut für Diabetesforschung
Helmholtz Zentrum München

und

Forschergruppe Diabetes
Klinikum rechts der Isar
Technischen Universität München

Lehrstuhl für Diabetes und
Gestationsdiabetes

und

Forschergruppe Diabetes e.V.
am Helmholtz Zentrum München

Annette Knopff
Telefon: 0800 - 3 38 33 39
Durchwahl: 089 / 3187 2546
Fax: 089 / 3187 3144
E-Mail:Annette.Knopff@helmholtz-muenchen.de
Teddy Deutschland: www.teddy-studie.de
Teddy: www.teddy.epi.usf.edu

München, 25.04.2018

Sehr geehrte Familie xxx,

vielen Dank für die Zusendung der Blutprobe.

Die Diabetes-Autoantikörperuntersuchung vom xxx bei xxx ergab folgendes Ergebnis:

Diabetes-Autoantikörper vom tt.mm.jjjj:

IAA:	positiv	Titer:		units (normal <0,95 units)
GADA:	positiv	Titer:		WHO units/ml (normal <33 WHO units)
IA2A:	positiv	Titer:		WHO units/ml (normal <5 WHO units)

Diabetes-Autoantikörper vom tt.mm.jjjj:

ZnT8A:	positiv	Titer:		units (normal <0,02 units)

Die Diabetes-Autoantikörper IAA, GADA, IA2 und ZnT8A sind bei xxx positiv.

Da alle Autoantikörper positiv sind, besteht ein frühes Stadium eines Typ 1 Diabetes. Das Risiko für erhöhte Blutzuckerwerte und eine notwendige Insulintherapie liegt bei etwa 70% innerhalb von 10 Jahren; das bedeutet, dass 70 von 100 Kindern mit mehreren Diabetes-Autoantikörpern innerhalb von 10 Jahren erhöhte Blutzuckerwerte entwickeln und mit der Insulintherapie beginnen müssen.

Wir wissen, dass Kinder, bei denen der Diabetes frühzeitig erkannt wird, bei Diagnose oft nur kurz oder eventuell gar nicht stationär im Krankenhaus aufgenommen werden müssen.

Daher testen wir die diabetesspezifischen Autoantikörper, den Blutzucker und den Langzeitblutzuckerwert HbA1c bei jeder TEDDY Untersuchung. Außerdem wird alle 6 Monate ein oraler Glukose-Toleranztest bei ihrem Kind durchgeführt, um den Typ 1 Diabetes rechtzeitig zu diagnostizieren.

Helmholtz Zentrum München
Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH)
Ingolstädter Landstr. 1
85764 Neuherberg
Telefon +49(0)89 3187 (0)
Telefax +49(0)89 3187 3322

info@helmholtz-muenchen.de
www.helmholtz-muenchen.de

Aufsichtsratsvorsitzende:
MinDir'in Bärbel Brumme-Bothe

Geschäftsführer:
Prof. Dr. Günther Wess
Dr. Alfons Enhsen

Registergericht:
Amtsgericht München HRB 6466
USt-IdNr- DE 129521671

Bankverbindung:
Münchner Bank eG
Konto-Nr. 2 158 620
BLZ 701 900 00
IBAN DE04701900000002158620
BIC GENODEF1M01

HelmholtzZentrum münchen
Deutsches Forschungszentrum für Gesundheit und Umwelt

Klinikum rechts der Isar

Technische Universität München

Lehrstuhl für Diabetes und Gestationsdiabetes

Wir empfehlen Ihnen weiterhin gelegentlich selbst Blutzuckermessungen (nüchtern und nach dem Frühstück) bei xxx vorzunehmen und auf mögliche, typische Symptome zu achten:

- ungewöhnlicher Gewichtsverlust
- vermehrter Durst
- häufiges Wasserlassen
- Einnässen
- Übelkeit, Erbrechen
- Kraftlosigkeit, Müdigkeit
- häufige Pilzinfektionen

Wir raten Ihnen diesen Befund auch mit Ihrem Kinderarzt zu besprechen. Er kann sich auch jederzeit gerne unter der kostenlosen Hotline bei uns melden.

Mit Hilfe der nächsten Untersuchung im Rahmen von TEDDY in ca. drei Monaten werden wir den Verlauf der Autoantikörper bei xxx weiterhin gerne beobachten.

Wenn Sie Fragen zum Testergebnis oder zur TEDDY-Studie haben, stehen wir Ihnen unter unserer kostenlosen Rufnummer 0800 – 3383339 gerne zur Verfügung.

Vielen Dank für Ihre tolle Mitarbeit an der TEDDY-Studie.

Mit freundlichen Grüßen

Ihre

_____ _____

Prof. Dr. med. Anette-G. Ziegler Joanna Stock

Univ.- Prof. Dr. med. Anette-Gabriele Zieg
Direktorin
Institut für Diabetesforschung
Helmholtz Zentrum München

und

Forschergruppe Diabetes
Klinikum rechts der Isar
Technischen Universität München

Lehrstuhl für Diabetes und
Gestationsdiabetes

und

Forschergruppe Diabetes e.V.
am Helmholtz Zentrum München

Annette Knopff
Telefon: 0800 - 3 38 33 39
Durchwahl: 089 / 3187 2546
Fax: 089 / 3187 3144
E-Mail:Annette.Knopff@helmholtz-muenchen.de
Teddy Deutschland: www.teddy-studie.de
Teddy: www.teddy.epi.usf.edu

Helmholtz Zentrum München
Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH)
Ingolstädter Landstr. 1
85764 Neuherberg
Telefon +49(0)89 3187 (0)
Telefax +49(0)89 3187 3322

info@helmholtz-muenchen.de
www.helmholtz-muenchen.de

Aufsichtsratsvorsitzende:
MinDir'in Bärbel Brumme-Bothe

Geschäftsführer:
Prof. Dr. Günther Wess
Dr. Alfons Enhsen

Registergericht:
Amtsgericht München HRB 6466
USt-IdNr- DE 129521671

Bankverbindung:
Münchner Bank eG
Konto-Nr. 2 158 620
BLZ 701 900 00
IBAN DE04701900000002158620
BIC GENODEF1M01

P8. SITE SPECIFIC LETTER FOR REPORTING MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: GEORGIA/FLORIDA (child's results) (used through August 2013)

Medical College of Georgia
GEORGIA'S HEALTH SCIENCES UNIVERSITY

TEDDY
Center for Biotechnology and Genomic Medicine
Medical College of Georgia
1120 15th Street,
Augusta, GA
Tel:1-888-225-7785
Tel:706-721-4161
Center for Biotechnology and Genomic Medicine
CA-4124
30912-2400

Date

Address

Dear (Parent Contact Name),

This is a follow-up letter to the telephone call we had about your child's autoantibody test results. Your child's test results are listed below.

Name of Autoantibody Test	Normal Level (US Sites)	Your Child's Results	Positive or Negative
IA-2A	$\leq$ 0.03 [index]		
GADA	$\leq$ 0.032 [index]		
IAA	$\leq$ 0.01 [index]		

As you can see, your child's results were positive or above normal for several autoantibodies. Because your child has tested positive for several autoantibodies more than once, we believe your child's risk for type 1 diabetes has significantly increased. Among children with your child's autoantibody testing results, we expect 50 out of 100 children will develop type 1 diabetes.

We will be carefully checking your child's blood glucose for diabetes at each TEDDY study visit. In the mean time, it is a good idea to watch your child carefully for any signs of type 1 diabetes. Things to look for include:

- ✓ Weight loss even though your child is eating a lot
- ✓ Increased thirst
- ✓ Peeing a lot
- ✓ Wetting the bed in a child who was previously dry
- ✓ Nausea
- ✓ Vomiting
- ✓ Frequent yeast infections
- ✓ No energy, feeling tired

We recommend you take your child to the doctor if these symptoms last more than a few days. We can send you more information about diabetes or you may find this information on our TEDDY website www.teddystudy.org.

You may like to share your child's test results with your child's doctor. We can give you a letter to take to your doctor explaining these results. We do NOT recommend that your child's test results be put in your child's medical record, as your child may never get diabetes. Feel free to give the doctor our toll free number and we will be glad to discuss your child's test results with your child's doctor.

If you have any questions or concerns, please call us on our toll free number _____.

Your next TEDDY study visit is scheduled for _____(provide date and time). We look forward to seeing you then.

Sincerely,

Doctor name

TEDDY Study Clinical Director

Study Coordinator Name

TEDDY Study Coordinator

P9. SITE SPECIFIC LETTER FOR REPORTING MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: GEORGIA/FLORIDA (child's results) (used August 2013 – September 2014)

Georgia Regents University
Medical College of Georgia
Center for Biotechnology and Genomic Medicine

TEDDY
Center for Biotechnology and Genomic Medicine
Medical College of Georgia
1120 15th Street, CA-4124
Augusta, GA 30912-2400

Tel: 1-888-225-7785
Tel: 706-721-4161
Fax: 706-721-3688

Date

Address

Dear (Parent Contact Name),

This is a follow-up letter to the telephone call we had about your child's antibody test results. Your child's test results are listed below.

Name of Antibody Test	Normal Level	Your Child's Results	Positive or Negative
IA-2A	≤ 0.03		
GADA	≤ 0.032		
IAA	≤ 0.01		
ZnT8A	≤ 0.020		

As you can see, your child's results were positive or above normal for several antibodies. Because your child has tested positive for several antibodies more than once, we believe your child's risk for type 1 diabetes has significantly increased. Among children with your child's antibody testing results, we expect 50 out of 100 children will develop type 1 diabetes.

We will be carefully checking your child's blood glucose for diabetes at each TEDDY study visit. In the mean time, it is a good idea to watch your child carefully for any signs of type 1 diabetes. Things to look for include:

- ✓ Weight loss even though your child is eating a lot
- ✓ Increased thirst
- ✓ Peeing a lot
- ✓ Wetting the bed in a child who was previously dry
- ✓ Nausea
- ✓ Vomiting
- ✓ Frequent yeast infections
- ✓ No energy, feeling tired

We recommend you take your child to the doctor if these symptoms last more than a few days. We

can send you more information about diabetes or you may find this information on our TEDDY website www.teddystudy.org.

You may like to share your child's test results with your child's doctor. We can give you a letter to take to your doctor explaining these results. We do NOT recommend that your child's test results be put in your child's medical record, as your child may never get diabetes. Feel free to give the doctor our toll free number and we will be glad to discuss your child's test results with your child's doctor.

If you have any questions or concerns, please call us on our toll free number _____.

Sincerely,

Doctor name

TEDDY Study Clinical Director

Study Coordinator Name

TEDDY Study Coordinator

P10. SITE SPECIFIC LETTER FOR REPORTING MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: GEORGIA/FLORIDA (child's results) (used September 2014 – November 2017)

GRU
GEORGIA REGENTS UNIVERSITY
AUGUSTA

Georgia Regents University
Medical College of Georgia
Center for Biotechnology and Genomic Medicine

TEDDY
Center for Biotechnology and Genomic Medicine
Georgia Regents University
1120 15th Street, CA-4124
Augusta, GA 30912-2400

Tel: 1-888-225-7785
Tel: 706-721-4161
Fax: 706-721-3688

Date

Address

Dear (Parent Contact Name),

This is a follow-up letter to the telephone call we had about your child's autoantibody test results. Your child's test results are listed below.

Name of Autoantibody Test	Normal Level	Your Child's Results	Positive or Negative
IA-2A	≤ 0.03		
GADA	≤ 0.032		
IAA	≤ 0.01		
ZnT8A	≤ 0.020		

As you can see, your child's results were positive or above normal for several diabetes autoantibodies.

This result indicates that your child's risk for getting type 1 diabetes is significantly increased. Based on these results, we estimate your child's risk of getting diabetes to be greater than 50%. This means out of 100 children, it is likely that 50 or more will go on to develop type 1 diabetes.

We will be carefully checking your child's blood glucose for diabetes at each TEDDY study visit. In the mean time, it is a good idea to watch your child carefully for any signs of type 1 diabetes. Things to look for include:

- ✓ Weight loss even though your child is eating a lot
- ✓ Increased thirst
- ✓ Peeing a lot
- ✓ Wetting the bed in a child who was previously dry
- ✓ Nausea
- ✓ Vomiting
- ✓ Frequent yeast infections
- ✓ No energy, feeling tired

You may like to share your child's test results with your child's doctor. We can give you a letter to take to your doctor explaining these results. Feel free to give the doctor our toll free number and we will be glad to discuss your child's test results with your child's doctor with your written permission.

If you have any questions or concerns, please call us on our toll free number _____.

Sincerely,

Doctor Name

TEDDY Study Clinical Director

Study Coordinator Name

TEDDY Study Coordinator

P11. SITE SPECIFIC LETTER FOR REPORTING MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: GEORGIA/FLORIDA (child's results) (used starting November 2017)

AUGUSTA UNIVERSITY

TEDDY

TEDDY Study
Center for Biotechnology and Genomic Medicine
Augusta University
1120 15th Street, CA-4124
Augusta, GA 30912-2400

Tel: 1-888-225-7785
Tel: 706-721-4161
Fax: 706-721-3688

Date

Address

Dear (Parent Contact Name),

This is a follow-up letter to the telephone call we had about your child's autoantibody test results. Your child's test results are listed below.

Autoantibody Test	Normal Level	Your Child's Results	Positive or Negative
IA-2A	≤ 5 [DK units/mL]		
GADA	≤ 20 [DK units/mL]		
IAA	≤ 0.01 [Index]		
ZnT8A	≤ 0.020 [Index]		

Your child has tested positive for multiple autoantibodies more than once. This result indicates that your child's risk for getting type 1 diabetes is significantly increased.

There are now many scientific studies that have followed children who have multiple autoantibodies. These studies tell us that your child's risk of getting diabetes in the next 10 years is greater than 70%. This means that out of 100 children with test results like your child's, 70 or more will develop type 1 diabetes in the next 10 years.

We know that when a child's type 1 diabetes is diagnosed early, the child receives treatment right away. Often, these children do not need to be hospitalized at the time of diagnosis. So, we will be checking your child's autoantibodies, blood glucose and hemoglobin A1c levels at each TEDDY study visit. We will also offer a special test – called an oral glucose tolerance test- every 6 months to check your child for type 1 diabetes.

We want you to watch your child carefully for any signs of type 1 diabetes. Things to look for include:

- ✓ Weight loss even though your child is eating a lot
- ✓ Increased thirst
- ✓ Peeing a lot
- ✓ Wetting the bed in a child who was previously dry
- ✓ Nausea
- ✓ Vomiting
- ✓ Frequent yeast infections
- ✓ No energy, feeling tired

We think it is a good idea to talk to your child's doctor about this. We can give you a letter to take to your doctor explaining these results. Feel free to give the doctor our number and we will be glad to discuss your child's test results with your child's doctor with your written permission.

If you have any questions or concerns, please call us at_____.

Sincerely,

Doctor Name

TEDDY Study Clinical Director

Study Coordinator Name

TEDDY Study Coordinator

P12. SITE SPECIFIC LETTER FOR REPORTING MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: WASHINGTON (child's results) (used August 2014 – July 2017)

PACIFIC NORTHWEST DIABETES RESEARCH INSTITUTE
720 Broadway • Seattle, Washington 98122 • 206-726-1200 • www.pndri.org

Date

Address

Dear (Parent Contact Name),

This is a follow-up letter to the telephone call we had about <child's name>'s autoantibody test results. Your child's test results are listed below.

Name of Autoantibody Test	Normal Level	Your Child's Results	Positive or Negative
IA-2A	≤ 5		
GADA	≤ 20		
IAA	≤ 0.01		
ZnT8A	≤ 0.020		

<Child's name> has tested positive for multiple autoantibodies more than once, which indicates that your child's risk for getting type 1 diabetes is significantly increased. Based on these results, we estimate your child's risk of getting diabetes to be greater than 50%. This means out of 100 children, it is likely that 50 or more will go on to develop type 1 diabetes.

We will be checking your child's autoantibodies and blood glucose levels at each TEDDY study visit. In the mean time, it is a good idea to watch your child carefully for any signs of type 1 diabetes. Things to look for include:

- ✓ Weight loss even though your child is eating a lot
- ✓ Increased thirst
- ✓ Peeing a lot
- ✓ Wetting the bed in a child who was previously dry
- ✓ Nausea
- ✓ Vomiting
- ✓ Frequent yeast infections
- ✓ No energy, feeling tired

You may like to share your child's test results with your child's doctor. We can give you a letter to take to your doctor explaining these results. Feel free to give the doctor our toll free number and we will be glad to discuss your child's test results with your child's doctor, with your signed permission.

If you have any questions or concerns, please call us on our toll free number 1-888-324-2140.

Sincerely,

Investigator Reporting Results
GRADE LEVEL 8.2

A-11 Multiple Persistent Autoantibody Letter Revised 4/7/2014

P13. SITE SPECIFIC LETTER FOR REPORTING MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: WASHINGTON (child's results) (used starting July 2017)

#16176097.0

PACIFIC NORTHWEST DIABETES RESEARCH INSTITUTE
720 Broadway • Seattle, Washington 98122 • 206-726-1200 • www.pndri.org

Date

Address

Dear (Parent Contact Name),

This is a follow-up letter to the telephone call we had about <child's name>'s autoantibody test results. Your child's test results are listed below.

Name of Test	Normal Level	Your Child's Level	Results
IA-2A	≤ 5		
GADA	≤ 20		
IAA	≤ 0.01		
ZnT8A	≤ 0.020		
HbA1c	≤6.0		

<Child's name> has tested positive for multiple autoantibodies more than once, which indicates that your child's risk for getting type 1 diabetes is significantly increased. Based on these results, we estimate your child has a 70% chance of developing diabetes in the next ten years.

We will be checking your child's autoantibodies and blood glucose levels at each TEDDY study visit. In the mean time, it is a good idea to watch your child carefully for any signs of type 1 diabetes. Things to look for include:

- ✓ Weight loss even though your child is eating a lot
- ✓ Increased thirst
- ✓ Peeing a lot
- ✓ Wetting the bed in a child who was previously dry
- ✓ Nausea
- ✓ Vomiting
- ✓ Frequent yeast infections
- ✓ No energy, feeling tired

We recommend you share these results with your child's doctor. Feel free to give the doctor our toll-free number and we will be glad to discuss your child's test results with your child's doctor, with your signed permission.

If you have any questions or concerns, please call us on our toll-free number 1-888-324-2140.

Sincerely,

Investigator Reporting Results
GRADE LEVEL 8.4

P14. SITE SPECIFIC LETTER FOR REPORTING MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: SWEDEN (child's results) (used September 2014 – June 2017)

Två eller flera Autoantikroppar 140930

Ditt barns blodprov har visat på två eller flera autoantikroppar vid mer än ett tillfälle. Detta innebär att ditt barns risk för att utveckla typ 1 diabetes har ökat betydligt. Utifrån dessa resultat uppskattar vi att ditt barns risk för typ 1 diabetes är mer än 50 %. Med detta menas att fler än 50 av 100 barn som har två eller flera autoantikroppar kommer att utveckla typ 1 diabetes.

Vi kommer att fortsätta kontrollera ditt barns autoantikroppar och även mäta glukos i blodet (kallas också blodsocker) vid varje TEDDY besök. Vi vill även göra er uppmärksamma på vilka symtom som kan vara tecken på diabetes.

Symtom att lägga märke till är:

- Ökad törst
- Kissar mycket och ofta
- Kissar i sängen efter det att barnet blivit torr på natten
- Viktminskning trots att barnet äter som vanligt
- Ökad trötthet, ingen energi
- Illamående
- Kräkningar
- Återkommande svampinfektioner

Har du frågor hör gärna av dig till din TEDDY sjuksköterska.

Autoantikropp	Referensvärde	Ditt barns resultat	Positivt/Negativt
IA-2A	< 5		
GADA	< 33		
IAA	≤ 0.95		
ZnT8A	≤ 0.020		

P15. SITE SPECIFIC LETTER FOR REPORTING MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY RESULTS: SWEDEN (child's results) (used starting June 2017)

TEDDY

Vid två eller flera autoantikroppar

Ert barns blodprov visar två eller flera autoantikroppar vid mer än ett tillfälle. Detta innebär att barnets risk för att få typ 1-diabetes har ökat betydligt. Det finns flera forskningsstudier som följt barn med autoantikroppar under längre tid än TEDDY. Utifrån dessa studiers resultat uppskattar vi att ert barns risk för typ 1-diabetes inom en 10 års period är 70 %. Med detta menas att 70 av 100 barn som har två eller flera autoantikroppar kommer att få typ 1-diabetes inom 10 år.

Vi kommer att fortsätta kontrollera ert barns autoantikroppar och blodglukos (kallas också blodsocker) vid varje TEDDY-besök. Vi kommer även att göra en Oral Glukos Tolerans Test (OGTT) var 6:e månad. En OGTT talar om för oss hur mycket insulin barnets betaceller avger till blodet.

Vi vill även göra er uppmärksamma på vilka symtom som kan vara tecken på diabetes.

Symtom att lägga märke till är:

- Ökad törst
- Kissar mycket och ofta
- Kissar i sängen efter det att barnet blivit torr på natten
- Viktminskning trots att barnet äter som vanligt
- Ökad trötthet, ingen energi
- Illamående
- Kräkningar
- Återkommande svampinfektioner

Har du frågor hör gärna av dig till din TEDDY – sjuksköterska

Autoantikropp	Referensvärde	Ditt barns resultat	Positivt/Negativt
IA-2A	< 5		
GADA	< 33		
IAA	≤ 0.95		
ZnT8A	≤ 0.020		

Q. MODEL LETTER FOR REPORTING ONE OR MORE NEGATIVE TEST RESULTS IN CASES WITH PREVIOUS MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY TEST RESULTS (child's results) – ADDED TO MOO – MAY 2017

Date
Address

Dear (Parent Contact Name),
This is a follow-up letter to the telephone call we had about your child's autoantibody test results. Your child's test results are listed below.

Name of Autoantibody Test	Normal Level – TEDDY Assay (US Sites)	Normal Level – TEDDY Assay (European Sites)	Normal Level– Harmonized Assay (US Sites)	Normal Level– Harmonized Assay (European Sites)	Your Child's Results	Positive or Negative
IA-2A	≤ 0.03 [index] – NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤ 9 WHO units/ml - NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤5	<5		
GADA	≤ 0.032 [index] - – NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤ 20 WHO units/ml - – NO LONGER USED IN TEDDY, HARMONIZED REPLACED	≤20	<33		
IAA	≤ 0.01 [index]	≤ 0.95 [index]	No harmonized assay; TEDDY assay will continue to be used	No harmonized assay; TEDDY assay will continue to be used		
ZnT8A	≤ 0.020					

As you know, your child previously tested positive for two or more autoantibodies. This means that your child's risk for getting type 1 diabetes is significantly increased. There are now many scientific studies that have followed children who have multiple autoantibodies. These studies tell us that your child's risk of getting diabetes in the next 10 years is greater than 70%. This means that out of 100 children with test results like your child's, 70 or more will develop type 1 diabetes in the next 10 years.

Your child's risk for diabetes has not gone down. Autoantibody results sometimes change over time. One of more negative autoantibody test results in children with have had two or more positive autoanitibody test results does not change the child's risk. Scientists are now studying such cases. Based on current scientific information, your child's risk for type 1 diabetes is NOT reduced.

We know that when a child's diabetes is diagnosed early, the child gets treated right away. Many of these children do not need to be hospitalized at the time of diagnosis. So, we will continue to check your child's

autoantibodies, blood glucose and hemoglobin A1C levels at each TEDDY study visit. We will also continue do an oral glucose tolerance test every 6 months to check your child for type 1 diabetes.

We want you to watch your child carefully for any signs of type 1 diabetes. Things to look for include:

- ✓ Weight loss even though your child is eating a lot
- ✓ Increased thirst
- ✓ Peeing a lot
- ✓ Wetting the bed in a child who was previously dry
- ✓ Nausea
- ✓ Vomiting
- ✓ Frequent yeast infections
- ✓ No energy, feeling tired

We think it is a good idea to talk to your child's doctor about this if you have not done so already. We can give you a letter to take to your doctor explaining your child's test results. Feel free to give the doctor our toll free number. We will be glad to discuss your child's test results with your child's doctor, with your signed permission.

If you have any questions or concerns, please call us on our toll-free number _____.

Sincerely,

GRADE LEVEL 8.1

R. MODEL MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY LETTER FOR PHYSICIAN (child's results) – EDITS MADE TO MODEL LETTER – MAY 2017

Doctor
123 Main Street
Anytown, WA 98123

Dear Dr._____,

Your patient, (CHILD) has been a research participant in the NIH funded TEDDY study (The Environmental Determinants of Diabetes in the Young) for (LENGTH OF TIME) after meeting inclusion criteria of increased genetic risk for developing type 1 diabetes due to HLA genotyping. Based on your patient's HLA genotyping alone, we estimate the child's risk for developing type 1 diabetes is 3% (for US general population; 14% for US first degree relatives).

We have been testing (CHILD'S NAME) for the presence of diabetes autoantibodies (GADA, IA-2A or IAA) as part of our protocol. (CHILD) has persistently become autoantibody positive for two or more of these autoantibodies.
This increases the child's risk for developing type 1 diabetes to approximately 70% within the next 10 years of the child's life; the child's lifetime risk is even higher.

As you know, this does not mean (CHILD) will develop diabetes for certain, but it does indicate the likelihood that the child will develop type 1 diabetes at some point in the future is very high. We have encouraged the child's parents to monitor the child for the signs and symptoms of diabetes. We also encourage parents to keep in close contact with their primary care physicians.

As part of this child's participation in the TEDDY study we will be monitoring autoantibody levels, conducting a random blood glucose measurement and measuring the child's hemoglobin A1c every 3 months at the child's TEDDY visit. We will also be conducting OGTTs on anevery 6 month basis.

(CHILD) parents have requested we send you this information.

If I can be of any assistance in the future regarding these results, please do not hesitate to call (xxxx) or email (xxx) me anytime.

Sincerely yours,

Site PI

S1.. SITE SPECIFIC MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY LETTER FOR PHYSICIAN: FINLAND (child's results)

Hyvä lääkäri/terveydenhoitaja,

seurannassasi oleva lapsi _____ on osallistunut NIH:n rahoittamaan **TEDDY-tutkimukseen** (The Environmental Determinants of Diabetes in the Young) _____ ajan siitä asti, kun hänellä vastasyntyneenä todettiin tutkimuksen sisäänottokriteerien mukainen suurentunut geneettinen diabetesalttius HLA-genotyypityksessä. Pelkästään HLA-genotyypin perusteella hänen riskinsä sairastua tyypin 1 diabetekseen on noin 7 % (Suomessa koko väestön sairastumisriski on 0,7 % ja diabetesta sairastavan henkilön 1. asteen sukulaisten riski noin 6 %)

Olemme määrittäneet häneltä tutkimusprotokollan mukaisesti diabetekseen liittyviä autovasta-aineita (GAD-, ICA512- ja IAA-vasta-aineet). Hänellä on nyt toistuvasti todettu kahta tai useampaa vasta-ainetta. Tämä lisää hänen riskiään sairastua tyypin 1 diabetekseen n. 50%:iin.

Kuten tiedätte, tämä ei tarkoita, että hänelle varmuudella kehittyisi tyypin 1 diabetes, mutta sen riski on selvästi suurentunut. Olemme suositelleet, että vanhemmat tarkkailevat mahdollisia diabeteksen oireita ja ovat tarvittaessa herkästi yhteydessä omaan lääkäriin tai terveydenhoitajaan.

TEDDY-tutkimuksen puitteissa seuraamme lapsen vasta-ainetasoja joka tutkimus-käynnillä. Seuraamme myös verensokeritasoja satunnaisilla mittauksilla ja teemme tietyin välein oraalisia glukoosirasituksia 3-vuotiaille ja sitä vanhemmille lapsille.

TEDDY-lapsen vanhemmat ovat pyytäneet, että lähetämme Sinulle nämä tiedot. Jos voimme olla näiden tulosten suhteen avuksi, voitte soittaa (puh.) tai olla meihin yhteydessä sähköpostitse _____millloin tahansa.

Kunnioittaen

Professori Olli Simell
TYKS Lastenklinikka

S2. SITE SPECIFIC MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY LETTER FOR PHYSICIAN: GERMANY (child's results)

Brief: für Arzt

Dr. .....

München, ...

Sehr geehrte Dr. .....,

Ihr/e Patient/in ……nimmt seit …. Monaten an der vom NIH geförderten TEDDY Studie (The Environmental Determinants of Diabetes in the Young) teil, nachdem ein erhöhtes genetisches Risiko für die Entwicklung eines Typ 1 Diabetes mittels HLA-Genotypisierung, diagnostiziert wurde. Allein aufgrund des HLA-Genotyps schätzen wir das Risiko des Kindes später einen Typ 1 Diabetes zu entwickeln auf 3% (bzw. 14%).

Im Rahmen des Studienprotokolls haben wir das Blut von …….. auf das Vorhandensein von Diabetes-assoziierten Autoantikörpern (GADA, IA-2A und IAA) untersucht. Dabei wurde bei ……. mehrmals eine Autoantikörperpositivität für einen oder mehrere dieser Autoantikörper festgestellt. Dieses Ergebnis erhöht das Typ 1 Diabetesrisiko bei …… auf ca. 50%.

Wie Sie sicher wissen, bedeutet das nicht, dass ..... auf jeden Fall einen Typ 1 Diabetes entwickeln wird, jedoch ist das Risiko dafür signifikant erhöht. Wir haben den Eltern empfohlen auf erste Anzeichen und Symptome eines Diabetes bei ..... zu achten. Wir empfehlen den Eltern auch in engem Kontakt mit Ihrem Kinder- oder Hausarzt zu stehen.

Im Rahmen der TEDDY Studie werden wir die Autoantikörper regelmäßig untersuchen. Wir werden auch die Blutglucosespiegel beobachten und ab einem Alter von 3 Jahren regelmäßige OGTTs durchführen.

Die Eltern von ..... haben uns gebeten Ihnen diese Informationen mitzuteilen. Wir raten allen TEDDY Teilnehmern die Forschungsergebnisse aus Vertraulichkeitsgründen nicht in die Krankenakte des Kindes aufnehmen zu lassen.

Falls Sie Fragen zu diesen Testergebnissen haben stehen wir Ihnen unter der gebührenfreien Telefonnummer 0800 / 33 8 333 9 sowie per email unter Teddy.Germany@lrz.uni-muenchen.de zur Verfügung.

Mit freundlichen Grüßen,

Prof. Dr. Anette-G. Ziegler Dr. med. Peter Achenbach

S3. SITE SPECIFIC MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY LETTER FOR PHYSICIAN: GEORGIA/FLORIDA (child's results)

TEDDY

Medical College of Georgia
GEORGIA'S HEALTH SCIENCES UNIVERSITY

Center for Biotechnology and Genomic Medicine

Center for Biotechnology and Genomic Medicine
Medical College of Georgia
1120 15th Street, CA-4124
Augusta, GA 30912-2400
Email:help@pandastudy.org
Tel:1-888-225-7785
Tel:706-721-4161
Fax:706-721-3688

Doctor
123 Main Street
Anytown, WA 98123

Dear Dr._____,

Your patient, (CHILD) has been a research participant in the NIH funded TEDDY study (The Environmental Determinants of Diabetes in the Young) for (LENGTH OF TIME) after meeting inclusion criteria of increased genetic risk for developing type 1 diabetes due to HLA genotyping. Based on your patient's HLA genotyping alone, we estimate the child's risk for developing type 1 diabetes is 3% (for US general population; 14% for US first degree relatives).

We have been testing (CHILD'S NAME) for the presence of diabetes autoantibodies (GADA, IA-2A or IAA) as part of our protocol. (CHILD) has persistently tested autoantibody positive for two or more of these autoantibodies. This increases the child's risk for developing type 1 diabetes to approximately 50%.

As you know, this does not mean (CHILD) will develop diabetes for certain, but it does indicate a significantly increased risk. We have encouraged the child's parents to monitor the child for the signs and symptoms of diabetes. We also encourage parents to keep in close contact with their primary care physicians.

As part of this child's participation in the TEDDY study, we will be monitoring autoantibody levels at every visit. We will also be monitoring blood glucose levels with random blood glucose measurements and with periodic OGTTs on children 3 years of age and older.

(CHILD) parents have requested we send you this information. We usually advise TEDDY participants to keep experimental research findings out of their medical records for confidentiality reasons.

If I can be of any assistance in the future regarding these results, please do not hesitate to call (xxxx) or email (xxx) me anytime.

Sincerely yours,
Doctor name

TEDDY Study Clinical Director

S4. SITE SPECIFIC MULTIPLE PERSISTENT POSITIVE AUTOANTIBODY LETTER FOR PHYSICIAN: WASHINGTON (child's results)

PACIFIC NORTHWEST RESEARCH INSTITUTE

Doctor
123 Main Street
Anytown, WA 98123

Dear Dr._____,

Your patient, (CHILD) has been a research participant in the NIH funded TEDDY study (The Environmental Determinants of Diabetes in the Young) for (LENGTH OF TIME) after meeting inclusion criteria of increased genetic risk for developing type 1 diabetes due to HLA genotyping. The risk of developing type 1 diabetes based on HLA alone is approximately 3%.

We have been testing (CHILD'S NAME) for the presence of diabetes autoantibodies (GAD, ICA 512 or IAA) as part of our protocol. CHILD) has persistently become (1, 2, or 3) autoantibody positive which has increased his/her risk to approximately (12% or 50%).

As you know, this does not mean (CHILD) will develop diabetes for certain, but it does indicate a significantly increased risk. We continue to educate all our increased risk subjects to the signs and symptoms of diabetes and encourage our subjects to keep in close contact with their primary physicians.

(CHILD) parents have requested we send you this information. We usually advise our subjects to keep experimental research findings out of their medical records for confidentiality reasons.

If I can be of any assistance in the future regarding these results, please do not hesitate to call (206-860-6759) or email (wah@u.washington.edu) me anytime.

Sincerely yours,

William A. Hagopian, MD, PhD,
Principal Investigator, Northwest TEDDY Study
Pacific NW Research Institute
206-860-6770
Toll Free: 1-888-324-2140

T1. SITE SPECIFIC MULTIPLE PERSISTENT POSITIVE ANTIBODY TO SINGLE PERSISTENT POSITIVE ANTIBODY LETTER: GEORGIA/FLORIDA (child's results) (used starting September 2014)

GRU
GEORGIA REGENTS UNIVERSITY
AUGUSTA

Georgia Regents University
Medical College of Georgia
Center for Biotechnology and Genomic Medicine

TEDDY
Center for Biotechnology and Genomic Medicine
Georgia Regents University
1120 15th Street, CA-4124
Augusta, GA 30912-2400

Tel: 1-888-225-7785
Tel: 706-721-4161
Fax: 706-721-3688

Date

Address

Dear (Parent Contact Name),

This is a follow-up letter to the telephone call we had about your child's autoantibody test results. Your child's test results are listed below.

Name of Autoantibody Test	Normal Level	Your Child's Results	Positive or Negative
IA-2A	≤ 0.03		
GADA	≤ 0.032		
IAA	≤ 0.01		
ZnT8A	≤ 0.020		

As you can see, your child's results were positive or above normal for at least one autoantibody. Because your child has tested positive for several autoantibodies more than once, we believe your child's risk for type 1 diabetes remains significantly increased. Among children with your child's autoantibody testing results, we expect 50 out of 100 children will develop type 1 diabetes.

We will be carefully checking your child's blood glucose for diabetes at each TEDDY study visit. In the mean time, it is a good idea to watch your child carefully for any signs of type 1 diabetes. Things to look for include:

- ✓ Weight loss even though your child is eating a lot
- ✓ Increased thirst
- ✓ Peeing a lot
- ✓ Wetting the bed in a child who was previously dry
- ✓ Nausea
- ✓ Vomiting
- ✓ Frequent yeast infections
- ✓ No energy, feeling tired

We recommend you take your child to the doctor if these symptoms last more than a few days. We

can send you more information about diabetes or you may find this information on our TEDDY website www.teddystudy.org.

You may like to share your child's test results with your child's doctor. We can give you a letter to take to your doctor explaining these results. We do NOT recommend that your child's test results be put in your child's medical record, as your child may never get diabetes. Feel free to give the doctor our toll free number and we will be glad to discuss your child's test results with your child's doctor.

If you have any questions or concerns, please call us on our toll free number _____.

Sincerely,

Doctor name

TEDDY Study Clinical Director

Study Coordinator Name

TEDDY Study Coordinator

U.PARENT INFORMATION SHEET WITH NO STAGING LANGUAGE

What is Type-1 Diabetes? (T1D)

Type 1 diabetes is one of the most common and serious long-term diseases in children.

- T1D is increasing worldwide. In (country), 1 in (country specific) children have T1D
- T1D occurs when the beta cells of the pancreas are destroyed by the body's own immune system. When the beta cells are destroyed, the body can no longer make insulin.
- When food is eaten it is broken down into glucose or sugar and goes into the blood. Every cell in the body needs to use that sugar for energy. Our pancreas has beta cells that make insulin. Insulin opens the body's cell walls so that sugar in the blood can enter. With insulin, our cells have energy and blood sugar levels remain normal.
- If there is no insulin, the body can't use the sugar from the food that is eaten. The sugar builds up in the blood. High blood sugar can cause serious illness or even death if not treated.
- Children with T1D must take insulin shots several times a day or wear an insulin pump. Right now, there is no cure forT1D.

What causes T1D?

- We don't know exactly what causes T1D. A person's genes and the environment seem to play a part. But people with no high-risk genes sometimes get T1D. Studies like TEDDY are helping to learn more about this.

How does T1D develop?

- Our body's immune system produces cells called antibodies to fight off germs. This helps us stay healthy. Sometimes the immune system makes a mistake and begins to produce antibodies that attack healthy parts of the body. This is called autoimmunity. The antibodies attacking healthy parts of the body are called autoantibodies.
- T1D is an autoimmune disease. The body's immune system produces autoantibodies that destroy the beta cells in the pancreas. These are the autoantibodies we test for in every study blood draw.

What is the process that leads to T1D?

- T1D starts before people have symptoms or high blood sugar levels
- The immune system begins to attack the beta cells in the pancreas. When this happens, we begin to see autoantibodies in the blood.
- When a person has two or more autoantibodies, their risk for diabetes increases. At this time, there are still a lot of healthy beta cells left. The body can produce enough insulin to keep blood sugar levels normal. There are no symptoms.
    - 70 out of 100 people with 2 or more autoantibodies will get T1D within 10 years.
    - People with 2 or more autoantibodies should learn to monitor blood sugars.
    - It is important for children with 2 or more antibodies to come to the TEDDY visits every 3 months to monitor the child's blood sugar.
    - High blood sugar may appear in response to a sugar challenge like a large meal
    - We will do an oral glucose tolerance test (OGTT) every 6 months to tells us if your child is progressing toward diabetes.
    - We will also test your child's Hemoglobin A1c (HA1C). HA1C measures a person's average blood sugar over the last 3 months. If your child's HA1C becomes higher, your child may be progressing toward diabetes.
- When most of a person's beta cells have been destroyed, the beta cells that are left cannot make enough insulin to keep the blood sugars normal. Symptoms of T1D occur, become more severe over time, and are life-threatening if medical treatment is not started.

Symptoms of T1D:

- Intense thirst
- Frequent urination
- Bedwetting (in child who was previously "dry")
- Weight loss
- Lack of energy
- Blurred vision
- Behavior changes
- Yeast infections

When a person with T1D is ill, under physical stress or taking steroids, blood sugars often become high. People with 2 or more autoantibodies should also check blood sugars more often during these times.

Symptoms such as confusion, heavy breathing or vomiting require urgent medical attention.

Grade level: 6.9

V1. SITE SPECIFIC PARENT INFORMATION SHEET WITH NO STAGING LANGUAGE: SWEDEN (Started using June 2017)

20170505

TEDDY

INFORMATION TILL ALLA FÖRÄLDRAR

Vad är typ 1-diabetes?

Typ 1-diabetes är en av de vanligaste allvarliga kroniska sjukdomarna hos barn.

- Typ 1-diabetes ökar över hela världen.
- Vår bukspottkörtel har betaceller som producerar insulin. Typ 1-diabetes uppstår när betacellerna i bukspottkörteln förstörs av kroppens eget immunförsvar. När betacellerna förstörts, kan kroppen inte längre tillverka insulin.
- Varje cell i kroppen behöver energi. Maten vi äter omvandlas till glukos (druvsocker) och transporteras ut i blodet. Insulin öppnar kroppens cellväggar så att glukos kan komma in i cellen. Med hjälp av insulin får våra celler energi och glukoshalten i blodet förblir normal.
- Om det inte finns tillräckligt med insulin, kan kroppens celler inte använda glukos. Blodglukos (i dagligt tal blodsocker) stiger eftersom glukos inte har någon annanstans att ta vägen. Högt blodglukos kan orsaka allvarlig sjukdom eller dödsfall om den inte behandlas.
- Personer med typ 1-diabetes måste ersätta det insulin som kroppen normalt producerar genom injektioner eller via en insulinpump.

Vad orsakar typ 1-diabetes?

- Vi vet inte exakt vad som är orsaken till typ 1-diabets. En persons arvsanlag (gener) och miljö tycks ha betydelse. Personer utan högriskgener kan också insjukna i typ 1-diabetes. Studier som TEDDY, bidrar till att lära oss hur typ 1-diabetes utlöses.

Hur utvecklas typ 1-diabetes?

Kroppens eget immunsystem har celler som producerar antikroppar för att bekämpa bakterier och virus. Detta hjälper oss hålla oss friska. Ibland gör immunsystemet ett misstag och börjar angripa friska celler i kroppen. Detta kallas autoimmunitet. Autoantikroppar (varningssignaler) i blodet visar att immunsystemet felaktigt angriper kroppen.

- Typ 1-diabetes är en autoimmun sjukdom. Kroppens immunsystem gör ett misstag och angriper betacellerna i bukspottkörteln. Vi kan mäta autoantikroppar i blodet för att se om detta händer. Detta görs vid varje besök på TEDDY.

Hur ser processen ut som leder till typ 1-diabetes?

- Typ 1-diabetes debuterar innan symtom eller höga blodglukosnivåer uppstår.

- Immunsystemets celler börjar angripa betacellerna i bukspottkörteln. När detta händer ökar antalet autoantikroppar i blodet.

1

• När en person har två eller flera autoantikroppar ökar risken för diabetes. Det finns fortfarande en hel del friska betaceller kvar och kroppen kan producera tillräckligt med insulin för normalt blodglukos. Det finns ännu inga symtom men de kommer när tillräckligt många betaceller har förstörts.

o 70 av 100 personer med 2 eller flera autoantikroppar får typ 1-diabetes inom 10 år.

o Det är viktigt för barn med 2 eller fler autoantikroppar att komma på TEDDY-besök var 3:e månad för kontroll av blodglukos.

o Högt blodglukos kan uppträda som svar på en "sockerutmaning" som en "stor" måltid t.ex. middagsmål.

o Vi kommer att göra en oral glukostoleranstest (OGTT) var 6:e månad på ert barn. Detta test berättar för oss om barnet är på väg att utveckla typ 1-diabetes.

o Vi testar också barnets HbA1c, som visar genomsnittligt blodglukos under de senaste 3 månaderna. Om HbA1c stiger, kan ditt barn vara på väg att få typ 1-diabetes.

• När de flesta betaceller har förstörts hos ett barn med två eller flera autoantikroppar, kan betacellerna som finns kvar inte producerar tillräckligt med insulin för att hålla en normal blodglukosnivå. Symtom på typ 1-diabetes uppstår och förvärras. Sjukdomen är livshotande och medicinsk behandling med insulin ska påbörjas.

Symtom på typ 1-diabetes:
• Intensiv törst
• Kissar ofta och stora urinmängder
• Sängvätning (barn som tidigare varit "torra")
• Viktminskning
• Brist på energi-trötthet
• Dimsyn
• Beteendeförändringar
• Svampinfektioner

Symtom som förvirring, tung andning eller kräkningar kräver brådskande läkarvård.

TIETOA TEDDY-TUTKIMUKSESTA

DIABETEKSEEN LIITTYVÄT VASTA-AINEET

Nykykäsityksen mukaan tyypin 1 diabetes syntyy, kun haiman insuliinituotanto vähitellen heikkenee ja loppuu. Tapahtuman käynnistävät tekijät ovat tuntemattomia, mutta taudin kehittymiseen liittyy valkosolujen välittämä ns. autoimmuunireaktio haiman insuliinia tuottavia beetasoluja vastaan. Kun insuliinia tuottavat solut vaurioituvat, niistä vapautuu solunsisäisiä valkuaisaineita. Valkosolumme alkavat muodostaa vasta-aineita niitä kohtaan. Näitä autovasta-aineita voidaan mitata verinäytteistä ja ne heijastavat haimassa tapahtuvaa beetasoluvauriota.

Tutkimuksessamme seurataan kolmea erilaista autovasta-ainetta, joilla on merkitystä diabetesriskin arvioinnissa:

- IAA (insulin autoantibodies eli insuliiniautovasta-aineet)
- GADA(glutamic acid decarboxylase antibodies eli glutamaattidekarboksylaasivasta-aineet)
- IA-2A (islet antigen 2 antibodies eli IA-2 vasta-aineet)

Lisäksi kaikilta, joille on kehittynyt jokin kolmesta edellä mainitusta autovasta-aineesta, tutkitaan neljäs autovasta-aine:

- ZnT8A (zinc transporter 8 antibodies eli sinkkitransportterivasta-aineet)

Vasta-aineiden ennustearvosta. Vaikka yleisesti ottaen voidaan sanoa, että autovasta-aineiden ilmaantuminen lisää lapsen vaaraa sairastua diabetekseen, lapsen muuttuminen vasta-ainepositiiviseksi ei tee hänestä sairasta. On hyvä muistaa, että vasta-ainetuloksista ei voida tehdä varmoja johtopäätöksiä yksittäisen lapsen kohdalla, eikä myöskään voida ennustaa mahdollista sairastumisajankohtaa. Mikäli

Versio 5 / 11.9.2017

verinäytteestä on löytynyt diabetekseen liittyviä vasta-aineita, lapsen seurantaa tehostetaan. Käytännössä tämä tarkoittaa, että jatkossa tutkimuskäynnit ovat lapsen iästä riippumatta 3 kk:n välein.

Ainoastaan **yhden** autovasta-ainetyypin esiintymiseen ei liity merkittävästi lisääntynyttä diabetesriskiä. Jos lapselle ilmaantuu **kaksi tai useampia** autovasta-aineita, hänen sairastumisriskinsä on selvästi kohonnut, noin 70 % sairastuu seuraavien 10 vuoden aikana. Jos enemmän kuin 2 vasta-ainetta ovat positiivisia ja lisäksi todetaan heikentynyt sokerinsieto sokerirasituskokeessa, sairastumisen riski on huomattavan suuri.

SOKERIRASITUSKOE (OGTT-koe)

Jos lapsella on kaksi tai useampia autovasta-aineita hänelle tehdään sokerirasituskoe (OGTT, oral glucose tolerance test). Se voidaan tehdä myös, jos lapsella on diabetekseen liittyviä oireita ja/tai hänellä on kohonneita verensokeriarvoja tai pitkäaikaista verensokeritasoa kuvaava HbA1c-arvo on poikkeava. Sokerirasituskokeen avulla saadaan tietoa lapsen sokeriaineenvaihdunnasta.

Sokerirasituskokeet tehdään TEDDY-tutkimuksen tiloissa, ja niistä sovitaan aina erikseen perheen kanssa. Sokerirasituskoe tehdään aina aamulla, koska tutkimukseen tullaan ravinnotta. Lapsen tulee olla ravinnotta edellisestä illasta (klo 22) lähtien. Kokeessa lapselta otetaan paastoverinäyte, jonka jälkeen lapsi juo sokeriliuosta (glukoosia) painon mukaisen annoksen. Tämän jälkeen seurataan sokeriarvoja kahden tunnin ajan. Sokerirasituskokeen perusteella voidaan todeta diabetes, vaikkei tyypillisiä oireita ole vielä ilmaantunut.

KUN JANOTTAA JA PISSATTAA…

Tyypin 1 diabeteksen oireita ovat väsymys, jano ja runsas virtsan eritys, tilanteen pitkittyessä myös laihtuminen. Pissalla on käytävä tavallista useammin ja usein pissahätä herättää myös yöllä, tai jo kuivaksi oppinut lapsi voi alkaa kastella uudelleen. Vaippaikäisellä vaippa voi olla jatkuvasti märkä. Jos insuliinipuute kestää pitempään, vaarana on ns. ketoasidoosin kehittyminen. Tällöin lapsella voi esiintyä mahakipuja ja pahoinvointia, hengitys voi muuttua raskaaksi ja siinä voi tuntua asetonin (kynsilakan poistoaineen) haju, ja lopulta lapsi voi muuttua tokkuraiseksi. On hyvä pitää mielessä, että hoitamaton diabetes on lapselle hengenvaarallinen tila.

Jos herää epäily lapsen sairastumisesta diabetekseen, ottakaa viipymättä yhteys tutkimusvastaanotolle tai lastentautien päivystykseen. Verensokeri tulee viipymättä mitata joko kotimittarilla tai vastaanotolla. Koholla oleva aterianjälkeinen arvo (≥11.1 mmol/l) tai paastoarvo (≥7.0 mmol/l) viittaa todennäköiseen diabetekseen. Virka-aikaan voitte ottaa yhteyttä TEDDY-tutkimuksen vastaanotolle (Turku puh. 02-313 3491 / Oulu puh. 08-315 5147 / Tampere puh. 03-3116 4086). Jos ette tavoita TEDDY-hoitajaa, tai epäilette sairastumista viikonloppuna tai ilta-aikaan, ottakaa yhteys suoraan Tyks/Oys/Tays lastentautien päivystyspoliklinikalle (puh. 02-313 1420/08-315 5260/03-311 65713).

Turun / Oulun / Tampereen TEDDY-tutkimusryhmän puolesta,

Jorma Toppari
Professori, ylilääkäri
Sähköposti: jorma.toppari@utu.fi

Riitta Veijola
Professori, ylilääkäri
Sähköposti: riitta.veijola@oulu.fi

Mikael Knip
Professori, ylilääkäri
Sähköposti: mikael.knip@helsinki.fi

Versio 5 / 11.9.2017

Mikä on tyypin 1 diabetes?

Tyypin 1 diabetes on yksi yleisimmistä ja vakavimmista pitkäaikaissairauksista lapsilla.

- Tyypin 1 diabeteksen (T1D) esiintyvyys on kasvussa ympäri maailmaa. Suomessa T1D on yleisempi kuin missään muualla maailmassa. Joka vuosi Suomessa sairastuu noin 500 alle 15-vuotiasta lasta ja 1500 yli 15-vuotiasta tyypin 1 diabetekseen.
- Tyypin 1 diabetes alkaa, kun kehon oma immuunipuolustus on tuhonnut haiman beetasolut. Kun beetasolut ovat hävinneet, elimistö ei enää pysty tuottamaan insuliinia.
- Syötyämme ruoka pilkotaan glukoosiksi ja se vapautuu verenkiertoon. Jokainen elimistön solu tarvitsee glukoosia energian lähteenä. Haiman beetasolut valmistavat insuliinia. Insuliini avaa soluseiniä siten, että glukoosi pääsee solun sisälle. Insuliinin erittymisen myötä soluilla on energiaa ja verensokeritaso pysyy normaalina.
- Jos insuliinia ei erity, elimistö ei pysty käyttämään ravinnosta saatavaa glukoosia, vaan glukoosi jää verenkiertoon. Korkea verensokeri voi aiheuttaa vakavan sairastumisen ja jopa kuoleman, mikäli sitä ei hoideta.
- Tyypin 1 diabetesta sairastavien lasten tulee ottaa useita insuliiniannoksia päivässä tai käyttää insuliinipumppua. Tällä hetkellä tyypin 1 diabetekseen ei ole parannuskeinoa.

Mikä aiheuttaa tyypin 1 diabeteksen?

- Emme vielä tarkkaan tiedä, mikä aiheuttaa tyypin 1 diabeteksen. Perimän ja ympäristötekijöiden uskotaan yhdessä vaikuttavan siihen, kuka sairastuu. Kuitenkin myös henkilöt, joilla ei ole kohonnutta geneettistä riskiä sairastua tyypin 1 diabetekseen voivat sairastua. TEDDY:n kaltaiset tutkimukset lisäävät ymmärrystämme niistä tekijöistä, jotka voivat johtaa taudin puhkeamiseen.

Miten tyypin 1 diabetes kehittyy?

- Elimistömme immuunipuolustus tuottaa vasta-aineita, joiden avulla se pystyy torjumaan erilaisia taudinaiheuttajien hyökkäyksiä. Tosinaan immuunijärjestelmämme tekee virheen ja se alkaa tuottaa vasta-aineita kehon omia, terveitä soluja vastaan. Tätä ilmiötä kutsutaan autoimmuniteetiksi. Vasta-aineita, joita on tuotettu kehon omia soluja vastaan, kutsutaan autovasta-aineiksi.
- Tyypin 1 diabetes on autoimmuunisairaus. Kun haiman insuliinia tuottavat solut vaurioituvat, niistä vapautuu solunsisäisiä valkuaisaineita. Valkosolumme alkavat muodostaa vasta-aineita niitä kohtaan. Näitä autovasta-aineita voidaan mitata verinäytteistä ja ne heijastavat haimassa tapahtuvaa beetasoluvauriota.

Mikä johtaa tyypin 1 diabeteksen syntyyn?

- Tyypin 1 diabetes alkaa jo ennen kuin henkilöllä on mitään oireita tai korkea verensokeri.
- Immuunijärjestelmä hyökkää haiman beetasoluja vastaan. Kun näin tapahtuu, pystymme havaitsemaan verestä autovasta-aineita.
- Kun henkilöllä on kaksi tai useampia autovasta-aineita, riski sairastua tyypin 1 diabetekseen kasvaa, vaikka haimassa on edelleen jäljellä paljon terveitä soluja. Elimistö voi edelleen tuottaa riittävästi insuliinia pitäen verensokeritason normaalina. Mitään oireita ei ole.
    - Henkilöllä, joilla on kaksi tai useampi autovasta-aine seitsemänkymmentä (70) sadasta (100) tulee sairastumaan tyypin 1 diabetekseen seuraavan kymmenen vuoden kuluessa.
    - Olisi hyvä, jos henkilöt, joilla on kaksi tai useampia autovasta-aineita seuraisivat verensokeritasoja.
    - On tärkeää, että lapset, joilla on kaksi tai useampia autovasta-aineita tulevat TEDDY-käynneille kolmen kuukauden välein verensokeritasojen seuraamiseksi.
    - Verensokeritaso voi nousta korkeaksi esim. ruokailun jälkeen.
    - Teemme sokerirasituskokeen (OGTT) kuuden kuukauden välein selvittääksemme, onko lapsellasi kehittymässä diabetes.
    - Määritämme lapseltanne myös hemoglobiini A1c-tason (HbA1c). HbA1c kertoo henkilön keskimääräisestä verensokeritasosta kuluneen kuuden viikon aikana. Jos lapsesi HbA1c nousee, lapsellasi on mahdollisesti kehittymässä diabetes.
    - Kun suurin osa beetasoluista on tuhoutunut, jäljellä olevat beetasolut eivät pysty enää tuottamaan tarpeeksi insuliinia pitääkseen verensokeritason normaalina. Tällöin ilmenevät tyypin 1 diabeteksen oireet, jotka ajan kuluessa pahenevat ja ovat henkeä uhkaavia, mikäli insuliinihoitoa ei aloiteta.

      Tyypin 1 diabeteksen oireet:

      - voimakas janontunne
      - kasvanut virtsaamisen tarve
      - yökastelua (lapsilla, jotka ovat aiemmin olleet jo ”kuivia”)
      - painon lasku
      - vetämätön olo
      - sumentunut näkö
      - käytösmuutokset
      - hiivatulehdukset

Kun tyypin 1 diabetesta sairastava henkilö tulee äkillisesti sairaaksi, on fyysisesti rasittunut tai käyttää kortisonilääkitystä, nousee usein myös verensokeri. Henkilöiden, joilla on kaksi tai useampia autovasta-aineita, tulisi myös tarkistaa verensokeritasot useammin yllä kuvatun kaltaisissa tilanteissa.

Sekavuus, raskas hengitys tai pahoinvointi ovat oireita, jotka vaativat välitöntä yhteydenottoa lääkäriin.

versio 2 (12.9.2017)

W. PARENT INFORMATION SHEET WITH STAGING LANGUAGE

What is Type-1 Diabetes? (T1D)

Type 1 diabetes is one of the most common and serious long-term diseases in children.

- T1D is increasing worldwide. In (country), 1 in (country specific) children have T1D.
- T1D occurs when the beta cells of the pancreas are destroyed by the body's own immune system. When the beta cells are destroyed, the body can no longer make insulin.
- When food is eaten it is broken down into glucose or sugar and goes into the blood. Every cell in the body needs to use that sugar for energy. Our pancreas has beta cells that make insulin. Insulin opens the body's cell walls so that sugar in the blood can enter. With insulin, our cells have energy and blood sugar levels remain normal.
- If there is no insulin, the body can't use the sugar from the food that is eaten. The sugar builds up in the blood. High blood sugar can cause serious illness or even death if not treated.
- Children with T1D must take insulin shots several times a day or wear an insulin pump. Right now, there is no cure forT1D.

What causes T1D?

- We don't know exactly what causes T1D. A person's genes and the environment seem to play a part. But people with no high-risk genes sometimes get T1D. Studies like TEDDY are helping to learn more about this.

How does T1D develop?

- Our body's own immune system produces cells called antibodies to fight off germs. This helps us stay healthy. Sometimes the immune system makes a mistake and begins to attack healthy parts of the body. This is called autoimmunity. Autoantibodies found in the blood tell us the immune system is attacking the body.
- T1D is an autoimmune disease. The body's immune system makes a mistake and attacks the beta cells in the pancreas. We can test for autoantibodies in the blood to tell us whether this is happening.

What is the process that leads to T1D?

In 2015, the Juvenile Diabetes Research Foundation (JDRF), the American Diabetes Association (ADA) and the Endocrine Society adopted a statement that describes 3 stages in the development of T1D. The statement recognizes the process of developing T1D starts before people have symptoms or high blood sugar levels

- **Stage 1** starts when a person has two or more islet autoantibodies. The immune system has begun to attack the beta cells in the pancreas. At this time, there are a lot of healthy beta cells left. The body is able to produce enough insulin to keep blood sugar levels normal. There are no symptoms.
    - People with stage 1 of T1D should learn to monitor blood sugars.
    - 70 out of 100 people in this stage will get T1D within 10 years.
    - It is important to come to the TEDDY visits every 3 months to monitor your child's blood sugar. Doing an oral glucose tolerance test (OGTT) every 6 months will tells us if your child has progressed to Stage 2.
- **Stage 2** starts when so many beta cells have been destroyed that the body is no longer able to keep blood sugars normal all the time. At this stage, people do not notice any symptoms.
    - High blood sugar may appear in response to a sugar challenge like a large meal or the OGTT. Hemoglobin A1c (HA1C) measures a person's average blood sugar over the last 3 months. During this stage, a person's HA1C may become higher.
- In **Stage 3,** most of the beta cells have been destroyed. The beta cells that are left cannot produce enough insulin to keep the blood sugars normal. Symptoms of T1D occur, become more severe over time, and are life-threatening if medical treatment is not started. At the stage, the person has T1D.

Symptoms of T1D:

- Intense thirst
- Frequent urination
- Bedwetting (in child who was previously "dry")
- Weight loss
- Lack of energy
- Blurred vision
- Behavior changes
- Yeast infections

When a person with T1D is ill, under physical stress or taking steroids, blood sugars often become high. People with any stage of T1D should check blood sugars more often during these times.

Symptoms such as confusion, heavy breathing or vomiting require urgent medical attention.

Grade level: 6.7

X1. SITE SPECIFIC PARENT INFORMATION SHEET WITH STAGING LANGUAGE: SWEDEN (Started using June 2017)

20170505

TEDDY

FÖRDJUPAD INFORMATION TILL ALLA FÖRÄLDRAR.

Vad är typ 1-diabetes?

Typ 1-diabetes är en av de vanligaste och allvarligaste kroniska sjukdomarna hos barn.
• Typ 1-diabetes ökar över hela världen.
• Vår bukspottkörtel har betaceller som producerar insulin. Typ 1-diabetes uppstår när betacellerna i bukspottkörteln förstörs av kroppens eget immunförsvar. När betacellerna förstörs, kan kroppen inte längre tillverka insulin.
• Varje cell i kroppen behöver energi. Maten vi äter omvandlas till glukos (druvsocker) och transporteras ut i blodet. Insulinet öppnar kroppens cellväggar så att glukos kan komma in i cellen. Med hjälp av insulin får våra celler energi och blodglukos förblir normalt.
• Om det inte finns insulin, kan kroppens celler inte använda glukos från maten och glukosnivån i blodet stiger. Högt blodglukos (blodsocker) kan orsaka allvarlig sjukdom eller dödsfall om den inte behandlas.
• Barn med typ 1-diabetes måste ta insulininjektioner flera gånger om dagen eller bära en insulinpump. Just nu finns det inget botemedel for typ 1-diabetes.

Vad orsakar typ 1-diabetes?
• Vi vet inte exakt vad som är orsaken till typ 1-diabetes. En persons gener och miljön tycks ha betydelse. Personer utan högriskgener kan också insjukna i typ 1-diabetes. Studier som TEDDY bidrar till att lära oss mer om detta.

Hur utvecklas typ 1-diabetes?
Kroppens eget immunsystem har celler som producerar antikroppar för att bekämpa bakterier och virus. Detta hjälper oss hålla oss friska. Ibland gör immunsystemet ett misstag och börjar angripa friska celler i kroppen. Detta kallas autoimmunitet. Autoantikroppar (varningssignaler) i blodet visar att immunsystemet felaktigt angriper kroppen.
• Typ 1-diabetes är en autoimmun sjukdom. Kroppens immunsystem gör ett misstag och angriper betacellerna i bukspottkörteln. Vi kan mäta autoantikroppar i blodet för att se om detta händer. Detta görs vid varje besök på TEDDY.

20170505

Hur ser processen ut som leder till typ 1-diabetes?
År 2015 antog, Juvenile Diabetes Research Foundation (JDRF), American Diabetes Association (ADA) och Endocrine Society ett uttalande som beskriver 3 steg i utvecklingen av typ 1-diabetes. Uttalandet bekräftar att typ 1-diabetes utvecklas innan symtom eller höga blodsockernivåer uppstår.

• **Steg 1** startar när en person har två eller flera autoantikroppar. Immunsystemet har börjat att angripa betacellerna i bukspottkörteln men det finns en hel del friska betaceller kvar. Kroppen kan producera tillräckligt med insulin för att hålla blodglukos normalt och det märks inga symtom.

o 70 av 100 personer i steg 1 kommer att få typ 1-diabetes inom 10 år.

o Det är viktigt att barnet kommer på TEDDY besök var 3:e månad för att kontrollera blodglukos och var 6:e månad för att göra ett oralt glukostoleranstest (OGTT). OGTT kan avslöja om sjukdomsprocessen gått vidare till **steg 2**.

• **Steg 2** startar när så många betaceller har förstörts att kroppen inte hela tiden kan hålla ett normalt blodglukos. I detta skede märks inga symtom.

o Högt blodglukos kan uppträda som svar på en ”glukosbelastning” som tex efter en stor måltid eller en OGTT (oral glukostoleranstest). Under ”Steg 2” kan en persons HbA1c-värde stiga. Hemoglobin A1c (HbA1c) mäter en persons genomsnittliga blodsocker under de senaste 3 månaderna. Under steg 2 kan Langerhanska öar drabbas av en inflammation som är en direkt attack på betacellerna.

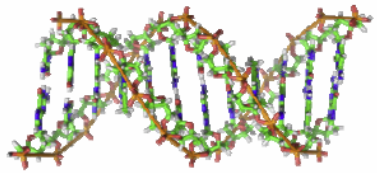
• **Steg 3** startar då de flesta beta-cellerna förstörts. Betacellerna som finns kvar kan inte producera tillräckligt med insulin för att hålla blodglukos normalt. Symtom på typ 1-diabetes uppstår och förvärras. Detta kan bli livshotande om inte medicinsk behandling med insulin påbörjas.

Symtom på typ 1-diabetes
• Intensiv törst
• Kissar ofta och stora urinmängder
• Sängvätning (barn som tidigare varit "torra")
• Viktminskning
• Brist på energi-trötthet
• Dimsyn
• Beteendeförändringar
• Svampinfektioner

När en person med typ 1-diabetes blir sjuk, är under fysisk stress eller tar steroider (kortison) är det stor risk att blodglukos blir för högt. Vid dessa tillfällen är det väldigt viktigt att personer som är i något av steg 1, 2 eller 3 av typ 1-diabetes kontrollerar sitt blodglukos oftare.

Symtom som förvirring, tung andning eller kräkningar kräver brådskande läkarvård.

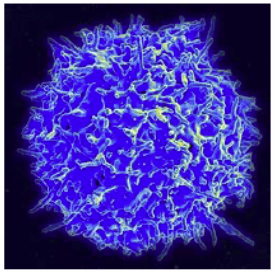
Y. Model TEDDY Diabetes



DNA: the genetic material

Genetic Risk

People who have certain genes or relatives with T1D have an increased risk of developing T1D



Picture of a human T-cell, part of the immune system

Immune Activation

The immune system of some people who are at increased risk for T1D may attack the beta cells in the pancreas. We can tell this is happening by doing a blood test and looking for autoantibodies.

How to monitor blood sugars

- Check your child's blood sugar at least 2-4 times a month; **daily if they are ill**.
- You can check blood sugars any time. But we recommend checking 2 hours after a large meal.
- .Always have your child wash their hands with soap and water before testing. This will prevent false readings.
- Blood sugar is considered within acceptable ranges at these levels:

On waking up (before breakfast)	80 to 120
Before meals	80 to 120
2 hours after meals (recommended)	180 or less
At bedtime	Less than 140

If blood sugar is > 200:

- Wash child's hands with soap and water
- Test again
- If still high, call your TEDDY clinic and your pediatrician.

Stages of developing Type 1 Diabetes (T1D)

What is type 1 diabetes (T1D)?

The beta cells in the pancreas make insulin. In T1D the immune system makes a mistake. It thinks the beta cells are "foreign" and attacks them. This is called autoimmunity. We can tell when this is happening by testing the blood for autoantibodies. If the autoimmune attack destroys too many beta cells, the person gets T1D.

What causes T1D?

We don't know exactly what causes a person's immune system to attack the beta cells. Both a person's genes and a person's environment seem to play a part. Studies like TEDDY are helping us learn more about this.

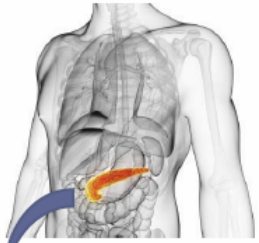
What are T1D stages?

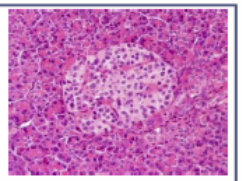
In 2015, the Juvenile Diabetes Research Foundation (JDRF), the American Diabetes Association (ADA) and the Endocrine Society adopted a statement that recognizes the disease process leading to T1D starts before people have symptoms or high blood sugar levels. The statement recognizes 3 stages of T1D.

Pamphlet

Stage 1

Location of the pancreas, which contains beta cells





A microscopic view of a healthy beta cells

Stage 1 of developing T1D starts when a person has two or more autoantibodies. The immune system has begun to attack the beta cells in the pancreas.

At this time, there are a lot of healthy beta cells left. The body is able to produce enough insulin to keep blood sugars normal. There are **no symptoms**.

People with stage 1 of T1D should learn to monitor blood sugars.

70 out of 100 people in this stage will get T1D within 10 years.

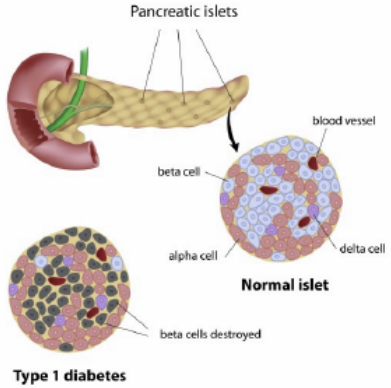
Stage 2

Checking a blood sugar using a glucometer.

Stage 2 starts when enough beta cells have been destroyed that the body is no longer able to keep blood sugars normal all of the time. At this stage, people do not notice any symptoms.

High blood sugar may appear in response to a sugar challenge like a large meal of the oral glucose tolerance test (OGTT). Hemoglobin A1c (HA1C) measures a person's average blood sugar over the last 3 months. During this stage, a person's HA1C may become higher.

Stage 3



Autoimmune attack destroys most of the beta cells of the pancreas

In stage 3, most of the beta cells have been destroyed. The beta cells that are left cannot produce enough insulin to keep the blood sugars normal. Symptoms of T1D occur, become more severe over time, and are life-threatening if medical treatment is not started. **Symptoms of T1D include:**

- **Intense thirst**
- **Frequent urination**
- **Bedwetting (in child who was previously "dry")**
- **Weight loss**
- **Lack of energy**
- **Blurred vision**
- **Behavior changes**
- **Yeast infections**

When a person with T1D is ill, under physical stress or taking steroids, blood sugars often become high. People with any stage of T1D should check blood sugars more often during these times. **If your child seems confused, is breathing heavily or is vomiting, get medical attention right away.**

Z. TEDDY RISK COMMUNICATION FREQUENTLY ASKED QUESTIONS (FAQs)

1. What happens after 10 years? Will my child still be at risk?

   It is not really known what happens. However, the risk does not disappear. There is not much research data available yet but that's why we are doing TEDDY so we can better understand this pattern.

2. Does it matter if my child has 2, 3 or 4 autoantibodies?

   Statistically the risk is comparable if a child has 2, 3 or 4 autoantibodies.

3. What if one or more autoantibodies go away? Does my child's risk go away?

   The risk does not go away if one or more autoantibodies go away after having had them for a long time.

4. What if child's autoantibody levels change? Does this mean my child's risk changes?

   Autoantibody levels can increase and decrease from one visit to the next. This means your child's risk does not change.

5. Which autoantibody is most common?

   IAA in young kids, GADA in teenagers and adults.

6. Does it matter which autoantibody comes first?

   No, what matters is that your child has two or more autoantibodies.

7. Is there an age when children are more likely to get diabetes?

   It is most likely between 5-7 years and during puberty.

8. Has puberty of any significance? Is the risk greater that my child develops T1D during puberty?

   The TEDDY study will find out but the hypothesis is that puberty is going to increase the risk for diabetes in those children who already have two or more autoantibodies.

9. Can we as a family do something for our children to prevent T1D?

   At present there is no known proven treatment that prevents the clinical onset of diabetes. Important to know the symptoms of diabetes. Alert your TEDDY clinic!

10. Are there prevention trials we could join?

    If you meet the participation criterial there may be locally available studies. We will tell you if we know of any trials that your child can join.

11. How long will you follow my child in TEDDY? What if TEDDY ends before 10 years? What happens after 10 years?

    Participation in current TEDDY study ends at the age of 15, there will be a proposal for a follow up study for however the specifics of this have not been identified as of yet.

AA1. Site Specific TEDDY Risk Communications Frequently Asked Questions (FAQs): Finland (Started using September 2017)

Usein kysytyt kysymykset - Riskikeskustelu

1. **Mitä tapahtuu kymmenen vuoden jälkeen? Onko lapseni edelleen vaarassa sairastua?**

   Vielä ei tarkkaan tiedetä, mitä tapahtuu kymmenen vuoden jälkeen. Lapsen riski sairastua ei kuitenkaan häviä. Tällä hetkellä asiasta ei ole vielä paljon tutkimustietoa saatavilla ja tämä onkin eräs syy, miksi TEDDY-tutkimusta tehdään.

2. **Onko merkitystä, jos lapsella on 2, 3 tai 4 vasta-ainetta?**
   Tilastollisesti riski kasvaa jonkin verran, mitä enemmän vasta-aineita on.

3. **Mitä, jos yksi tai useampi vasta-aine häviää? Häviääkö samalla lapseni riski sairastua?**

   Riski ei poistu, vaikka yksi tai useampi vasta-aine häviäisi oltuaan lapsella pitkään.

4. **Mitä, jos lapsen vaste-ainetasot muuttuvat? Tarkoittaako tämä sitä, että lapseni riski sairastua muuttuu?**

   Vasta-ainetasot voivat nousta tai laskea käynnistä toiseen. Tämä tarkoittaa, että lapsesi riski ei muutu.

5. **Mikä autovasta-aine on yleisin?**

   Pienillä lapsilla IAA on yleisin, teini-ikäsillä ja aikuisilla GADA.

6. **Onko sillä merkitystä, mikä autovasta-aine tulee ensin?**
   Ei ole. Merkityksellistä on se, onko lapsella kaksi tai useampia autovasta-aineita.

7. **Onko olemassa jotain ikää, jolloin lapset todennäköisimmin sairastuvat diabetekseen?**

   Sairastuminen voi tapahtua missä iässä tahansa.

versio 1/ 12.9.2017

BB1. Model Unable to Test for All Autoantibodies due to Insufficient Volume Letter (child's results): Colorado

Barbara Davis Center for Childhood Diabetes
The University of Colorado at Denver and Health Sciences Center
4200 East 9th Avenue, C-245
Denver, Colorado 80262

Parent's Name
Address
Address
TEDDY ID

Dear Parents (or person who signed the informed consent),

We are writing to tell you about the autoantibody test results from (CHILD'S NAME)'s TEDDY study visit on (DATE OF LAST CLINIC VISIT) _____.

Due to technical difficulties we were not able to test for all autoantibodies.

Autoantibody Test	Your Child's Result	Normal Level	Meaning
IA-2/ICA 512	Unable to test	<	inconclusive
GAD65	Unable to test	<	inconclusive
IAA	-0.000	<	negative

A negative result means there is no change in your child's risk for developing type 1 diabetes. As discussed before, we expect 3 out of 100 (14 out of 100) children who have the same genetic test results will develop the disease. Because we were not able to test your child for all 3 autoantibodies it is possible that his/her risk may be slightly higher.

Autoantibodies can appear at anytime in childhood. They usually occur 1 to 2 years before the onset of diabetes. We will continue to test your child at each TEDDY visit. As always, all tests are free of charge and your participation in TEDDY is voluntary.

If you have any questions about these test results or the TEDDY study, please call us at 303-724-7577. We will contact you soon about your next appointment, so please be sure let us know if you have a change of address or phone number.

Thank you for taking part in this diabetes study. We look forward to seeing you at your next clinic visit.

Sincerely,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

CC. MODEL MATERNAL BLOOD DRAW INFORMED CONSENT FORM

The Environmental Determinants of Diabetes in the Young - TEDDY Study

RESEARCHERS' STATEMENT

We are asking you to be in a research study. The purpose of this consent form is to give you the information you will need to help you decide whether or not to participate in the study. Please read the form carefully. You may ask questions about the purpose of the research, what we will ask you to do, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions, you can decide if you want to be in the study or not. This process is called 'informed consent'. We will provide a copy of this form for your records.

PURPOSE AND BENEFITS

The purpose of this research study is to gain more information on the development of insulin dependent diabetes. Insulin-dependent diabetes occurs most often in young people and in families without a history of diabetes. It occurs when the body stops producing enough insulin, which is a protein hormone made in the pancreas. The start of high blood sugar levels in people with insulin dependent diabetes is fairly quick. However, we know that the disease has usually been going on in the pancreas for several years before the diabetes becomes obvious, that is, before blood sugar levels rise. If the pancreas gets attacked by the immune system, it produces less and less insulin, eventually causing diabetes.

We are asking for a blood sample from you because your child is part of TEDDY and one of the following conditions is present.

- You have type 1 diabetes
- You have type 2 diabetes
- You had gestational diabetes during your most recent pregnancy
- Your baby tested positive for one or more of the diabetes autoantibodies at the 3 or 6-month clinic visit

It is possible that your child's positive test result may be because autoantibodies from you were transferred through the placenta. In most cases like this, your child's results will return to normal at later testing. We are asking for your sample to better analyze and understand your child's risk of developing type 1 diabetes. We would like to draw a small blood sample to see if you have these diabetes associated markers. Participation is entirely voluntary. The testing itself cannot cause diabetes.

The information gained may improve our knowledge about insulin-dependent diabetes. This information may be of future benefit to persons at risk for developing this disease by leading to better treatments or possibly a cure. Therefore, one benefit you may receive from this study is satisfaction in helping to prevent diabetes in others. If you do not currently have diabetes, you may test for one or more markers predictive of future diabetes risk. Some of these individuals may develop diabetes in the future, and may benefit from knowing their diabetes risk ahead of time. However, the markers only indicate risk of future diabetes, and cannot tell if a person will or won't get diabetes for sure.

PROCEDURES

A single blood draw (15 cc or approx. 1 tablespoonful) will be drawn from a vein in your arm. Your sample will be examined for several immune markers of diabetes [autoantibodies or immune cells (T-cells)]. The results of these tests will take 2 to 3 months to be completed.

Once the test results for these markers have been completed one of the investigators will contact you by telephone to explain what this means whether you test positive or negative. You may be offered the opportunity to have repeat blood sampling for autoantibody testing. This will be explained to you in detail by one of the investigators. You are only agreeing to one test at this time. You will be asked to consent to any future testing at the time of the future test. Participation in the marker screening test and the immune cell test are all entirely voluntary.

RISKS, STRESSES, OR DISCOMFORTS

When taking the blood sample, the needle insertion may cause temporary discomfort, and a bruise may form where the needle enters the vein. It is theoretically possible that participation in this diabetes prediction study might hurt your access to health insurance if information about your involvement and/or results of the study becomes part of your medical record. Therefore, we will keep all study data separate from your medical record. In addition, samples will be coded and strict confidentiality will be maintained by the study investigators. Subjects will be advised to keep their test results confidential.

You may find it stressful or upsetting to be notified of your test results. This may affect the way you view your health. These tests only reveal future risk and do not tell if you will get diabetes for sure. Therefore, we ask that these results do not change the way you view your health or supercede any advice from your physician. Eating sweets does not cause Type 1 diabetes. If at any time you have questions or concerns or change your mind about the selections you make on this form you may contact one of the members of the research team listed above.

OTHER INFORMATION

Being in this study is voluntary. There are no costs to you for taking part in this study. All information about you or your child and the linking code for the samples or results will be kept for up to 15 years. All data will be coded and kept private in locked files, in a locked building. Only researchers at this site will have the code linking your child's sample with any personal information. All samples will be sent to a central laboratory (repository) for storage and future use, if you agree. No information about you or your child will be given to the repository. These samples will be used for research only. If there is any remaining sample after completion of the study, all links to your information will be destroyed. Those samples will be completely anonymous. You will not receive money if any commercial products are made. At the end of the study, the code linking your sample will be destroyed. Only TEDDY study personnel, the National Institutes of Health, and the X Institutional Review Board that oversees the rights and protection of human subjects can see your results. You are free to refuse any question and/or withdraw from the research study at any time, for any reason, with no penalty. You can do this by contacting any of the researchers listed at the top of this consent form.

Your health records are considered protected health information. These health records can include results of medical exams, blood, genetic, stool, or urine tests, and family histories. Only members of the TEDDY study team and the Institutional Review Board have the legal right to see your research records. We will not show your research records to anyone without your permission.

When we talk about the study at scientific meetings, we will never use your name or your child's name. When we write about the study in scientific journals, we will never use your name or your child's name.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Even with the Certificate of Confidentiality, the investigators continue to have ethical and legal obligations to report child abuse or neglect and to prevent you from carrying out any threats to do serious harm to yourself or others. If keeping information private would immediately put you or someone else in danger, the investigators would release information to protect you or another person.

Department of Health and Human Services (DHHS) personnel may request identifying information for purposes of performing audits, carrying out investigations of DHHS grant recipients, or evaluating DHHS funded research projects.

SUBJECT'S STATEMENT

This study has been explained to me. I agree to take part in this research. I also agree to participate by answering questions about myself, including questions about any stress or anxiety I might be experiencing. I have been told that I can refuse to answer any question and I may withdraw from the study at any time without penalty. I have had a chance to ask questions. I have been told that future questions I may have about the research will be answered by one of the researchers listed on this form. If I have questions about my rights as a research subject, I can call the "X" Institutional Review Board at 1-XXX-XXX-XXXX. I will receive a copy of this consent form.

_____

Printed name of subject

_____

Signature of parent

_____ _____

Printed name of parent Date

I agree by initialing below that:

____ I am willing be contacted about other diabetes related studies

INVESTIGATOR'S STATEMENT

To the best of my knowledge, the subject understands the study goals, and risks and benefits. The subject has had all questions satisfactorily answered. The subject has voluntarily agreed to participate in this study. The subject understands all participation is voluntary. The subject received a copy of this consent.

_____

Signature of researcher

_____ _____

Printed name of researcher Date

Copy to: Subject
Investigator's file

DD. MODEL TELEPHONE SCRIPT FOR REPORTING MATERNAL AUTOANTIBODY NEGATIVE RESULTS

TEDDY Study
Reporting Autoantibody-Negative Results by Phone
(Mom Negative for Autoantibody Markers)

"Hello, my name is _____ and I am calling from the TEDDY Study. May I speak with _____? Do you have a few minutes to talk?"

[if yes continue. If no, record when to re-call and then say goodbye.]

"Back on _____ we took a blood sample from you because your child, _____, had tested positive for a diabetes autoantibody. We analyzed your sample for the same autoantibodies. As you may recall, your child's sample came back positive for the _____ autoantibody. When we tested your sample it came up negative for the autoantibodies. Since your baby tested positive and you tested negative, your child's results may indicate your child's immune system has started the inappropriate attack on the insulin producing cells. The best thing that we can do at this point is to watch your child and retest him/her at the next clinic visit. Autoantibodies that remain present at multiple samplings reveal a greater diabetes risk than ones that later go away.

"Since _____ is at an increased risk, you may wish to share these results with your doctor. However, we still recommend that they NOT be put in the medical record, as it is not definite that s/he will get diabetes. If your doctor has any additional questions, feel free to give him/her my name and number and I will be glad to answer them.

"You may remember that we explained previously that your child's risk is about 3 out of 100 (14 out of 100 ***for FDR families***) as compared to the general population's risk of 3 out or 1,000 (3 out of 100 ***for FDR families***). These autoantibody results may indicate that _____'s risk has increased, but it is important that we follow-up with another autoantibody sample from your child, which we will get at your next clinic visit.

"It may also be helpful to know the early warning symptoms of Type 1 diabetes. That way, if s/he gets diabetes, it can be recognized and treated right away at a milder stage. Would you like me to go over these possible symptoms with you?

[If not, skip the next paragraph]
[If so] Some of the early signs of Type 1 diabetes are: unexpected weight loss, being unusually thirsty, and frequent urination (to the point where one cannot sleep through the night), and feeling tired and uncomfortable. Often these symptoms very much resemble the flu, and can last for several days. Since your child may be at increased risk, I would recommend seeing your doctor if you/they get these symptoms and they last for more than a couple of days. We can also send you more information about diabetes from the American Diabetes Association or you may view their web site at: www.diabetes.org.

"It is also possible that, over time, the autoantibodies can go away and your child's risk of diabetes would then be less. Or new ones can show up suggesting his/her risk of diabetes has increased. For this reason, we would like to re-test your child at the next clinic visit. This is so we can get the best idea of your child's exact chance of getting diabetes and to help us understand the disease process. Do you have any questions at this point? If you have any questions later you can reach me at ___-___-____.

EE. MODEL TELEPHONE SCRIPT FOR REPORTING MATERNAL AUTOANTIBODY POSITIVE RESULTS (SAME MARKER AS INFANT)

TEDDY Study
Reporting Autoantibody-Positive Results by Phone
(Mom Positive for the Same Marker as Infant)

"Hello, my name is _____ and I am calling from the TEDDY Study. May I speak with _____? Do you have a few minutes to talk?"

[if yes continue. If no, record when to re-call and then say goodbye.]

"Back on _____ we took a blood sample from you because your child, _____, had tested positive for a diabetes autoantibody. We analyzed your sample for the same autoantibodies. As you may recall, your child's sample came back positive for the _____ autoantibody. When we tested your sample it came up positive for the same autoantibody. Since _____ is under one year of age, this most likely means that these were autoantibodies from you transferred in utero (before birth). However, it is not guaranteed that _____'s immune system has not started to attack the insulin producing cells. The best thing that we can do at this point is to watch your child and retest him/her at the next clinic visit. Autoantibodies that remain present at multiple samplings reveal a greater diabetes risk than ones that later go away.

"Since you tested positive for an autoantibody, this may mean that your risk of getting type 1 diabetes is increased. However, because you are an adult, and most cases are diagnosed during adolescence, your risk is not as great as we had reported for your child. Just like we explained for your child, the autoantibodies can change over time and so you may test negative at a later time. **(Site Specific Repeat Testing -** *This is a note for the individual center to put in their procedures. Many of the sites have other studies that the mom may qualify for based on these results and this would be the appropriate place to discuss them with her. Many individuals will want to be tested later to see if the autoantibodies change, but this is not part of TEDDY.**)***

"Since you are at an increased risk, you may wish to share these results with your doctor. However, we still recommend that they NOT be put in your medical record, as it is not definite that you will get diabetes. If your doctor has any additional questions, feel free to give him/her my name and number and I will be glad to answer them.

"You may remember that we explained previously that your child's risk is about 3 out of 100 (14 out of 100 ***for FDR families***) as compared to the general population's risk of 3 out or 1,000 (3 out of 100 ***for FDR families***). Based upon these test results we do not think your child's risk has changed, but it is important that we continue to monitor _____'s autoantibody status.

"It may also be helpful to know the early warning symptoms of Type 1 diabetes. That way, if you get diabetes, it can be recognized and treated right away at a milder stage. Would you like me to go over these possible symptoms with you?"

[If not, skip the next paragraph]
[If so] Some of the early signs of Type 1 diabetes are: unexpected weight loss, being unusually thirsty, and frequent urination (to the point where one cannot sleep through the night), and feeling tired and uncomfortable. Often these symptoms very much resemble the flu, and can last for several days. Since you/your child are at increased risk, I would recommend seeing your doctor if you/they get these

symptoms and they last for more than a couple of days. We can also send you more information about diabetes from the American Diabetes Association or you may view their web site at: www.diabetes.org.

"It is also possible that, over time, the autoantibodies can go away and your and your child's risk of diabetes would then be less. Or new ones can show up suggesting the risk of diabetes has increased. For this reason, we would like to offer re-testing for your child at the next clinic visit. This is so we can get the best idea of your child's exact chance of getting diabetes and to help us understand the disease process. Do you have any questions at this point? If you have any questions later you can reach me at ___-___-____."

FF. MODEL TELEPHONE SCRIPT FOR REORTING MATERNAL AUTOANTIBODY POSITIVE RESULTS (DIFFERENT MARKER THAN INFANT)

TEDDY Study
Reporting Autoantibody-Positive Results by Phone
(Mom Positive for a Different Marker than Infant)

"Hello, my name is _____ and I am calling from the TEDDY Study. May I speak with _____? Do you have a few minutes to talk?"

[if yes continue. If no, record when to re-call and then say goodbye.]

"Back on _____ we took a blood sample from you because your child, _____, had tested positive for a diabetes autoantibody marker. We analyzed your sample for the same diabetes risk markers. As you may recall, your child's sample came back positive for the _____ risk markers. When we tested your sample it came up positive for a different marker, _____. Since these are two different markers, your child's results may indicate that your child's immune system has started the inappropriate attack on the insulin producing cells. The best thing that we can do at this point is to watch your child and retest him/her at the next clinic visit. Autoantibodies that remain present at multiple samplings reveal a greater diabetes risk than ones that later go away.

"Since you tested positive for an autoantibody marker, this may mean that your risk of getting type 1 diabetes is increased. However, because you are an adult, and most cases are diagnosed during adolescence, your risk is not as great as we had reported for your child. Just like we explained for your child, the autoantibodies can change over time and so you may test negative at a later time. **(Site Specific Repeat Testing -** *This is a note for the individual center to put in their procedures. Many of the sites have other studies that the mom may qualify for based on these results and this would be the appropriate place to discuss them with her. Many individuals will want to be tested later to see if the autoantibodies change, but this is not part of TEDDY.)*

"Since you are at an increased risk, you may wish to share these results with your doctor. However, we still recommend that they NOT be put in your medical record, as it is not definite that you will get diabetes. If your doctor has any additional questions, feel free to give him/her my name and number and I will be glad to answer them.

"It may also be helpful to know the early warning symptoms of Type 1 diabetes. That way, if you get diabetes, it can be recognized and treated right away at a milder stage. Would you like me to go over these possible symptoms with you?

[If not, skip the next paragraph]
[If so] Some of the early signs of Type 1 diabetes are: unexpected weight loss, being unusually thirsty, and frequent urination (to the point where one cannot sleep through the night), and feeling tired and uncomfortable. Often these symptoms very much resemble the flu, and can last for several days. Since you/your child are at increased risk, I would recommend seeing your doctor if you/they get these symptoms and they last for more than a couple of days. We can also send you more information about diabetes from the American Diabetes Association or you may view their web site at: www.diabetes.org.

"It is also possible that, over time, the autoantibodies can go away and your or your child's risk of diabetes would then be less. Or new ones can show up suggesting the risk of diabetes has increased. For

this reason, we would like to re-test your child at the next clinic visit. This is so we can get the best idea of your child's exact chance of getting diabetes and to help us understand the disease process. Do you have any questions at this point? If you have any questions later you can reach me at ___-___-____."

GG. MODEL PHONE SCRIPT FOR REPORTING POSITIVE CELIAC DISEASE AUTOANTIBODY RESULTS

Bolded italicized items are for the benefit of the study personnel, and are not spoken!

Hi, I'm RESEARCHER from TEDDY Study. May I speak with PARENT?
Do you have a few minutes to talk? ***If not, ask when is good time to reach parent, note time to call back:_____.***

As you may recall, at your last TEDDY Clinic visit we did an additional test that we run once a year for celiac disease markers.

Celiac disease is an autoimmune disease like childhood diabetes. However, instead of the pancreas, the intestine is affected by an inflammation. This results in poor absorption of food nutrients and may be accompanied by persistent diarrhea. Symptoms of celiac disease may be less easy to notice than diabetes.

Your child's blood sample tested positive for the celiac disease markers (autoantibodies against transglutaminase). This may not mean for sure that your child has celiac disease, but there may be a risk of it in the future. Therefore, we would like to check a second blood sample.

It may be helpful to let your child's doctor know about these results so that he or she can watch your child for signs of celiac disease. If your child has celiac disease, it is well controlled by avoiding gluten (wheat protein) in the diet. However, it is important that you do not exclude gluten from the diet by yourself since your doctor is the only one who can determine if this is needed. Do you have any questions about celiac disease or your child's risk?

We will send you a letter explaining the test results. You may wish to show the letter to your child's doctor at your next regularly scheduled visit, or sooner if your child is not feeling well. Please phone us toll free at SITE SPECIC if any questions or concerns arise later.

Thank you. Bye.

Celiac Disease INFORMATION SHEET

What is celiac disease?

Celiac disease, or gluten intolerance as it is sometimes called, is a disease resulting from sensitivity to gluten in the diet. This can lead to problems with the small intestine, such as poor absorption of food. Gluten is especially abundant in grains such as wheat, rye and barley.

Like other immune diseases such as Type 1 diabetes, both genetic and environmental factors play a role in celiac disease. Besides the ingestion of gluten, some scientists think that a "trigger" sets off celiac disease in certain people. A trigger might be a virus, causing gastroenteritis.

What is gluten and how does it contribute to celiac disease?

Gluten is a plant protein found in certain grains and grain products, e.g. bread (whole grain or white), pasta and cookies. Plant gluten sticks to cells in the intestines. Sometimes, this confuses the immune system. The immune system then mistakenly attacks the small bowel causing celiac disease. The disease is inactive as long as there is no gluten in the diet.

What are the symptoms of celiac disease in children?

Gluten sensitivity is not the same thing as wheat allergy, although some people have both conditions. Babies with celiac disease often have diarrhea. They may not grow or gain weight at normal rates. Older children and adults with celiac disease may have diarrhea or hard stools or constipation. Some have only gas or bloating. Other symptoms of celiac disease are pain in the lower tummy or fatigue due to anemia. In many patients symptoms develop in childhood, but in others, they may not develop until later in life. Some individuals have very vague symptoms or report no symptoms from the gastrointestinal tract, although the small bowel is affected by celiac disease.

Why is my child at risk for celiac disease?

Your child tested positive for autoantibodies to transglutaminase. This is an enzyme found primarily in the intestines. When these autoantibodies are found in the blood, it usually means that there is autoimmunity against the intestines, that is, the small bowel mucosa is damaged. However, this may or may not turn into full celiac disease. About 1 in 100 children develop celiac disease. Children developing symptoms should be evaluated by a doctor for possible celiac disease.

Approximately 10% are at risk to develop celiac disease among first-degree relatives. It is therefore recommended that siblings and parents of a child with celiac disease also are tested for autoantibodies to transglutaminase.

How should I proceed with medical care for my child?

You should discuss these results with your doctor. The only way to diagnose celiac disease is by doing a biopsy of the intestine wall. We suggest that you discuss this test further when you take your child in to see the doctor. If your child develops diarrhea for several weeks or unexplained weight loss, he/she should definitely be seen by your doctor right away for possible celiac disease. The good news about celiac disease is that if your child does develop it, symptoms can be controlled by avoiding wheat and other gluten-containing products in the diet. A dietitian

can help design a diet that meets your child's needs should it become necessary. You should consult your physician before changing your child's diet. Advice and follow-up with a doctor is important. It is also important that the child does not follow the gluten-free diet before the diagnosis has been confirmed by biopsy.

Your doctor may be interested in the results of the transglutaminase test (so called IgA-tTG) before further investigation with a confirming biopsy. A normal result is below or equal to 0.05 units (USA) or below 1.3 units (Europe). Your child´s blood test showed:

Sample number	Date of sample	IgA-tTG test result (units)	Positive/Negative
1			
2			

II. MODEL LETTER FOR REPORTING POSITIVE CELIAC DISEASE AUTOANTIBODY RESULTS

Parent Doe
123 Main Street
Anytown, WA 98123

Dear _____,

This letter follows the phone call we made to you last week. It's about the results of the celiac test on CHILD's blood sample.

As we mentioned on the phone, CHILD's test was positive for the celiac autoantibodies against transglutaminase. This does **not** mean that s/he will have or get celiac disease for certain. However, his/her risk is increased. Therefore, I recommend that your child is further examined by a pediatrician for celiac disease.

Please read the enclosed information on celiac disease. Children with celiac markers can be watched closely for symptoms, which can then be found and treated at a milder stage. These symptoms can range from lack of growth to persistent diarrhea. We suggest that you discuss this letter with your child's doctor or nurse, so that they may be aware of these results.

If you have any additional questions, please feel free to call us at: SITE SPECIC.

Sincerely yours,

Site PI

GRADE LEVEL 7.5

JJ1. SITE SPECIFIC LETTER FOR REPORTING POSITIVE CELIAC DISEASE AUTOANTIBODY RESULTS: COLORADO

Parent's Name
Address
Address
TEDDY ID

Dear Parents (or person who signed the informed consent),

Thank you for taking the time to speak with us about (CHILD'S NAME) transglutaminase (TG) autoantibody test results. As we talked about on the phone, your child's autoantibody test results from the (DATE OF LAST CLINIC VISIT) visit are listed below.

TGIGA: 0.1234 Positive (Transglutaminase Autoantibody)

The transglutaminase autoantibody is used to screen people for celiac disease. Celiac disease is an autoimmune disease caused by a reaction to gluten, a protein found in wheat and wheat products A test result greater than 0.05 is considered positive for the screening. The positive test does NOT mean that your child definitely has celiac disease; it indicates that your child may have an increased risk of developing celiac disease in the future. The TEDDY Study will continue testing your child for this autoantibody on a yearly basis. As always, all tests are free of charge and taking part in TEDDY is voluntary.

We strongly recommend that you speak with your child's pediatrician for a referral to a pediatric gastroenterologist to discuss your options for further testing and follow up care. In the mean time, we would like for you to be aware of the symptoms associated with celiac disease:

- Abnormally gassy/burpy or bloated
- Abdominal pain
- Chronic diarrhea
- Constipation
- Weight loss/weight gain
- Fatigue
- Canker sores
- Anemia (a low count of red blood cells causing fatigue)
- Bone or joint pain
- Delayed growth or failure to thrive in infants
- Itchy skin rash called dermatitis herpetiformis

If you have any questions about these test results or the TEDDY study, please call us at 303-724-7577. We will contact you soon about your next appointment, so please let us know if you have a change in address or phone number.

Thank you for taking part in this study. We look forward to seeing you at your next visit.

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

JJ2. SITE SPECIFIC LETTER FOR REPORTING POSITIVE CELIAC DISEASE AUTOANTIBODY RESULTS: GERMANY

Brief: erstmals positiv

Familie .....

München, ...

Sehr geehrte Familie .....,

die Zöliakie-Antikörperuntersuchung vom ..... bei Ihrem Kind ..... (geb. .....) ergab folgende Werte:

Antikörpertest	**Normalbereich**	**Antikörperergebnis Ihres Kindes**	**Positiv oder Negativ**
Transglutaminase			

Wie bereits telefonisch besprochen, fiel der Zöliakie-Antikörpertest bei ……. positiv aus. Es bedeutet nicht, dass Ihr Kind in jedem Fall Zöliakie entwickeln wird. Das Risiko an einer Zöliakie zu erkranken ist jedoch erhöht. Deshalb empfehlen wir Ihr Kind von Ihrem Kinder- oder Hausarzt auf Zöliakie hin untersuchen zu lassen.

Bitte lesen Sie beiligendes Zöliakie-Informationsblatt. Bei Kindern mit Zöliakie-Antikörpern ist es empfehlenswert auf erste Anzeichen einer Zöliakie zu achten, so dass die Krankheit in einem frühen Stadium erkannt und behandelt werden kann. Die Symptome können von einer Wachstumsverzögerung/-störung bis hin zu einem anhaltenden Durchfall variieren. Wir schlagen Ihnen deshalb vor beiliegendes Informationsblatt genau mit Ihrem Kinder- oder Hausarzt zu besprechen, so dass dieser davon unterrichtet ist.

Falls Sie Fragen haben, können Sie uns unter der gebührenfreien Telefonnummer 0800 / 33 8 333 9 kontaktieren.

Mit freundlichen Grüßen,

Prof. Dr. Anette-G. Ziegler Dr. med. Peter Achenbach

JJ3. SITE SPECIFIC LETTER FOR REPORTING POSITIVE CELIAC DISEASE AUTOANTIBODY RESULTS: GEORGIA

Medical College of Georgia
GEORGIA'S HEALTH SCIENCES UNIVERSITY

Center for Biotechnology and Genomic Medicine

TEDDY
Center for Biotechnology and Genomic Medicine
Medical College of Georgia
1120 15th Street, CA-4124
Augusta, GA 30912-2400

Tel:1-888-225-7785
Tel:706-721-4161
Fax:706-721-3688
Email:help@pandastudy.org

Date

Dear (TEDDY Parent),

As you know, the goal of the TEDDY study is to identify the environmental triggers of type 1 diabetes. Diet monitoring is an important part of TEDDY, in part because children with diabetes are more likely than children without diabetes to have an intestinal condition called celiac disease (pronounced seal-ee-ak). Celiac disease is the result of a sensitivity to a major component of wheat and other grains, called gluten. Children with the most severe form of the condition grow poorly, because their intestine does not absorb fat normally. The mild forms of celiac disease may not cause any noticeable problems.

Because there may be a link between the gluten sensitivity causing celiac disease and type 1 diabetes, TEDDY researchers have tested your child's blood for autoantibodies that are linked to celiac disease. These are called transglutaminase autoantibodies. The result was positive. This does not mean your child necessarily has celiac disease or needs any treatment right now. We recommend that you show this letter to your child's doctor, especially if you are concerned that your child is not gaining enough weight or is having chronic diarrhea with greasy stools. If you prefer, one of our TEDDY doctors will (with your permission) be happy to speak with your doctor about the meaning of this test result.

Please, if you have any questions, do not hesitate to call us.

Sincerely,

(appropriate TEDDY physician and coordinator)

JJ4. SITE SPECIFIC LETTER FOR REPORTING POSITIVE CELIAC DISEASE AUTOANTIBODY RESULTS: FLORIDA

UNIVERSITY OF FLORIDA

Dept of Pediatrics
Diabetes Research Program
College of Medicine

PO Box 100296
Gainesville, FL 32610-0296
Tel: (352) 334-0843
Toll free: (800) 749-7424 ext. 334-0843
FAX: (352) 334-3870

Date

«GreetingLine»
«Address_Line_1»
«City», «State» «ZIP_Code»

RE: «childs_name»

Dear «salutation»,

This is a follow-up to our discussion about «childs_name»'s celiac disease test results. As we mentioned on the phone, «childs_name» was positive for the autoantibodies against transglutaminase. This does **not** mean that «childs_name» has or will get celiac disease for certain. However, the risk is increased. Therefore, I recommend that «childs_name» be further evaluated by your doctor for celiac disease.

Please read the enclosed information on celiac disease. Children with celiac markers can be watched closely for symptoms, which can then be found and treated at a milder stage. These symptoms can range from lack of growth to persistent diarrhea. We suggest that you discuss this letter with «childs_name»'s doctor or nurse, so that they may be aware of these results.

Your next TEDDY study visit is scheduled for _____. We look forward to seeing you then – but please don't hesitate to call at any time if you have any questions.

Sincerely yours,

Angie Choate
TEDDY Study Coordinator

Desmond Schatz, MD
Professor of Pediatrics

JJ5. SITE SPECIFIC LETTER FOR REPORTING POSITIVE CELIAC DISEASE AUTOANTIBODY RESULTS: WASHINGTON

PACIFIC NORTHWEST RESEARCH INSTITUTE

Date

Parent Doe
123 Main Street
Anytown, WA 98123

Dear *Parent's Name*,

This letter is to report the celiac test results from your last TEDDY study clinic visit. We'd like to thank you for taking part in this important study.

Child's Name tested **positive** for the autoantibody markers for celiac disease. There is no guarantee, but the results suggest that your child may be developing celiac disease.

As we discussed on the phone, Celiac Disease is an autoimmune disease that shares similar genetic markers with type 1 diabetes. Celiac Disease damages the small intestine and interferes with absorption of nutrients from food. People who have celiac disease cannot tolerate a protein called gluten, found in wheat, rye, and barley. Since *child's name* inherited the risk markers for type 1 diabetes they may have also inherited the risk markers for Celiac Disease, because of this relationship we tested *child's name* for autoantibodies for Celiac Disease. It may be helpful to let your child's doctor know about these results so they can watch your child for signs of Celiac Disease.

We will test your child again in 6 months at their clinic visit. All tests are provided completely free of charge, and your participation is entirely voluntary.

Someone from our research team will contact you in about 2 months to schedule your next appointment. If you have any questions before we contact you again, or if you do not wish to participate in the future, please feel free to contact us at 1-888-324-2140. Also, please contact us if you have a change of address or phone number.

Sincerely yours,

William A. Hagopian, MD, PhD,
Principal Investigator, Northwest TEDDY Study
Pacific NW Research Institute
206-860-6770
Toll Free: 1-888-324-2140

KK. MODEL LETTER FOR REPORTING POSITIVE CELIAC DISEASE AUTOANTIBODY RESULTS TO PEDIATRIC GASTROENTEROLOGIST

Dear Doctor

_____ is being referred to you for evaluation of possible celiac disease due to a positive IgA-anti-tTG (tissue transglutaminase) autoantibody test, which was performed as part of a study, called TEDDY (The Environmental Determinants of Diabetes in the Young). In this study, over 6000 children have been recruited in the US and several European countries in order to evaluate risk factors for the development of Type 1 Diabetes mellitus and celiac disease.

Participants of the study are screened for autoantibodies on a regular basis, including IgA-anti-tTG (tissue transglutaminase). The measurements are performed in a central laboratory with a high quality control.

Who is referred for intestinal biopsies?
If a positive titer is confirmed after at least 3 months in a second blood sample, the child is referred to a pediatrician or pediatric gastroenterologist where available. It is suggested that the diagnosis is confirmed by an intestinal biopsy if either the child has moderate or high titres (at least 5 times upper limit of normal) and/or has symptoms suggestive of celiac disease. The upper limit of normal for IgA-anti-tTG analyzed in TEDDY is $\leq$0.05 units (in USA) or <1.3 units (in Europe). In asymptomatic children, the optimal level for intestinal biopsy is with a TG autoantibody level $\geq$0.5 units (in USA) and $\geq$30 units (in Europe) to help maximize the chances of finding intestinal abnormalities. In symptomatic children with a positive IgA-anti-tTG result, intestinal biopsy is to be considered regardless of level. The result of the IgA-anti-tTG test is as below:

Sample number	Date of sample	IgA-tTG test result (units)	Positive/Negative
1			
2			

In order to have an accurate histological diagnosis, we would kindly ask the providing gastroenterologist to consider the following suggestions:

1. **At least 6 biopsies** should be taken: two each from the **duodenal bulb, the first and second part of duodenum,** because some children may have only villous atrophy in the duodenal bulb (Bonamico et al. J Pediatr Gastroenterol Nutr 2008;47(5):618-22). If shorten or absent villi are suspected from certain areas during endoscopy, these areas should be preferentially sampled.
2. If possible, proper orientation of the biopsies is highly recommended before they fixed and embedded in paraffin.
3. The histological findings should be reported according to the MARSH-Criteria.
4. Please provide a copy of the endoscopy and pathology report to the parents

Thank you for your kind cooperation.
Signature

LL1. SITE SPECIFIC LETTER FOR REPORTING NEGATIVE CELIAC DISEASE AUTOANTIBODY RESULT AFTER A POSITIVE CELIAC DISEASE AUTOANTIBODY RESULT: COLORADO

Parent's Name
Address
Address
TEDDY ID

Dear Parents (or person who signed the informed consent),

Thank you for taking the time to speak with us about (CHILD'S NAME) transglutaminase (TG) autoantibody test results. As we talked about on the phone, your child's autoantibody test results from the (DATE OF LAST CLINIC VISIT) visit are listed below.

TGIGA: 0.001 Negative (Transglutaminase Autoantibody)

The transglutaminase autoantibody is used to screen people for celiac disease. Celiac disease is an autoimmune disease caused by a reaction to gluten, a protein found in wheat and wheat products.

It is important to realize that even though the result suggests that the precursors of celiac disease are not occurring at this time, in the past your child has been positive for this autoantibody.

Even though your child's tests were negative at this visit, TG autoantibodies can appear at anytime in childhood. We will continue to test your child yearly through the TEDDY Study. As always, all tests are free of charge and your participation in TEDDY is voluntary.

If you have any questions about these test results or the TEDDY study, please call us at 303-724-7577. We will contact you soon about your next appointment. Please be sure let us know if you have a change of address or phone number.

Thank you for taking part in the TEDDY study. We look forward to seeing you at your next clinic visit.

Sincerely,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

MM1. SITE SPECIFIC LETTER FOR REPORTING NEGATIVE CELIAC DISEASE AUTOANTIBODY RESULTS: COLORADO

Parent's Name
Address
Address
TEDDY ID

Dear Parents (or person who signed the informed consent),

At (CHILD"S NAME)'s last TEDDY Study visit on (DATE OF LAST CLINIC VISIT) we tested his/her blood for the transglutaminase (TG) autoantibody. The transglutaminase autoantibody is used to screen people for celiac disease. Celiac disease is an autoimmune disease caused by a reaction to a protein found in wheat and wheat products.

We are writing to tell you that the result of the transglutaminase (TG) autoantibody test was negative.

The negative results give us 95% confidence that celiac disease is not occurring in your child at this time.

Even though your child's tests were negative at this visit, TG autoantibodies can appear at anytime in childhood. We will continue to test your child each year through the TEDDY Study. As always, all tests are free of charge and your participation in TEDDY is voluntary.

If you have any questions about these test results or the TEDDY study, please call us at 303.724.7577. We will contact you soon about your next appointment. Please be sure let us know if you have a change of address or phone number.

Thank you for taking part in the TEDDY study. We look forward to seeing you at your next clinic visit.

Sincerely,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

MM2. SITE SPECIFIC LETTER FOR REPORTING NEGATIVE CELIAC DISEASE AUTOANTIBODY RESULTS: GEORGIA/FLORIDA

Medical College of Georgia
GEORGIA'S HEALTH SCIENCES UNIVERSITY

Center for Biotechnology and Genomic Medicine

TEDDY
Center for Biotechnology and Genomic Medicine
Medical College of Georgia
1120 15th Street, CA-4124
Augusta, GA 30912-2400

Tel:1-888-225-7785
Tel:706-721-4161
Fax:706-721-3688
Email:help@pandastudy.org

Dear «Salutation»,

Thank you for your continued participation in the TEDDY type 1 diabetes study. As part of the services we offer through the TEDDY study, we will routinely test your child's blood sample for the protein markers associated with celiac disease. Type 1 diabetes and celiac disease are both autoimmune diseases, and are influenced by some of the same genes. We believe that children at risk for developing type 1 diabetes may also be at risk for developing celiac disease. We are pleased to report that your child's result for this celiac test was negative. A negative test at this time does not mean your child cannot develop celiac disease in the future. We will continue to test your child once a year for the signs of celiac disease, as part of your regular TEDDY tests.

Celiac disease, or celiac sprue as it is sometimes called, is a disease resulting from sensitivity to gluten in the diet. Gluten is found in grain foods such as wheat, rye and barley. Sensitivity to gluten can lead to problems with the small intestine, such as poor absorption of food. Babies with celiac disease often have diarrhea. They may not grow or gain weight at normal rates. Older children and adults with celiac disease may have diarrhea or greasy stools. Some people have constipation or hard stools. Some have only gas or bloating. Other symptoms of celiac disease are pain in the lower tummy and anemia. In many patients, symptoms develop in childhood, but in others, they may not develop until later in life. Some individuals have very vague symptoms or report no symptoms from the gastrointestinal tract, although the small bowel is affected by celiac disease. If your child experiences any of these symptoms, please discuss them with your pediatrician right away.

Please don't hesitate to call if you have any questions. We appreciate your help and support in this important study. We are working diligently for the prevention of diabetes and your willingness to participate will assist us in gaining the information we need to achieve this goal.

Regards,

MM3. SITE SPECIFIC LETTER FOR REPORTING NEGATIVE CELIAC DISEASE AUTOANTIBODY RESULTS: WASHINGTON

PACIFIC NORTHWEST RESEARCH INSTITUTE

Date

Parent Doe
123 Main Street
Anytown, WA 98123

Dear *Parent's Name*,

This letter is to report the celiac test results from your last TEDDY study clinic visit. We'd like to thank you for taking part in this important study.

Child's Name tested **negative** for the autoantibody markers for celiac disease. This news is reassuring. There is no guarantee, but the results suggest that your child is not developing celiac disease at this time.

As we discussed at your last visit, Celiac Disease is an autoimmune disease that shares similar genetic markers with type 1 diabetes. Celiac Disease damages the small intestine and interferes with absorption of nutrients from food. People who have celiac disease cannot tolerate a protein called gluten, found in wheat, rye, and barley. Since **child's name** inherited the risk markers for type 1 diabetes they may have also inherited the risk markers for Celiac Disease, because of this relationship The TEDDY Study annually tests **child's name** for autoantibodies for Celiac Disease.

Even though *Child's Name* tested negative for celiac markers, the markers can appear later in childhood. A child may develop celiac without having the markers, but this is rare. We will continue to test your child yearly at their clinic visits. All tests are provided completely free of charge, and your participation is entirely voluntary.

Someone from our research team will contact you in about 2 months to schedule your next appointment. If you have any questions before we contact you again, or if you do not wish to participate in the future, please feel free to contact us at 1-888-324-2140. Also, please contact us if you have a change of address or phone number.

Sincerely yours,

William A. Hagopian, MD, PhD,
Principal Investigator, Northwest TEDDY Study
Pacific NW Research Institute
206-860-6770
Toll Free: 1-888-324-2140

NN1. SITE SPECIFIC LETTER FOR REPORTING POSITIVE CELIAC DISEASE AUTOANTIBODY RESULT AFTER CELIAC DISEASE DIAGNOSIS: COLORADO

To the parents of: 01/01/01
JANE DOE
100 MAIN STREET 100000
DENVER, CO 80000

Dear Parents,

We are writing to tell you about the transglutaminase (TG) autoantibody test results from JANE's TEDDY study visit on 12/1/2009. The results of this test are positive.

TGIGA: 0.09 Positive (Transglutaminase Autoantibody)

The transglutaminase autoantibody is used to screen people for celiac disease. A test result greater than 0.05 is considered positive for the screening.

Please keep in mind if your child has been diagnosed with celiac disease, the transglutaminase autoantibody level can be used to monitor an individual's response to a gluten free diet. If JANE is on a gluten free diet, the transglutaminase level may gradually decrease to low positive or normal level within 6 months to 2 years. The TEDDY Study will continue testing your child for this autoantibody on a yearly basis. As always, all tests are free of charge and taking part in TEDDY is voluntary.

If you have any questions about these test results or the TEDDY study, please call us at 303-724-7577. We will contact you soon about your next appointment, so please let us know if you have a change in address or phone number.

Thank you for taking part in this study. We look forward to seeing you at your next visit.

Sincerely,

Marian Rewers, MD, PhD
Principal Investigator, TEDDY Study

OO1. SITE SPECIFIC LETTER FOR REPORTING NEGATIVE CELIAC DISEASE AUTOANTIBODY RESULT AFTER CELIAC DISEASE DIAGNOSIS: COLORADO

To the parents of: 01/01/01
JANE DOE
100 MAIN STREET 100000
DENVER, CO 80000

Dear Parents,

We are writing to tell you about the transglutaminase (TG) autoantibody test results from JANE's TEDDY study visit on 12/1/2009. The results of this test are negative.

TGIGA: 0.01 Negative (Transglutaminase Autoantibody)

Please keep in mind since your child has been diagnosed with celiac disease, the transglutaminase autoantibody level can be used to monitor an individual's response to a gluten free diet. JANE's autoantibody level indicates compliance with the gluten free diet. The TEDDY Study will continue testing your child for this autoantibody on a yearly basis. As always, all tests are free of charge and taking part in TEDDY is voluntary.

If you have any questions about these test results or the TEDDY study, please call us at 303-724-7577. We will contact you soon about your next appointment, so please let us know if you have a change in address or phone number.

Thank you for taking part in this study. We look forward to seeing you at your next visit.

Sincerely,

Marian Rewers, MD, PhD
Principal Investigator, TEDDY Study

PP. Newsletter, Announcement or Script description of the rational for adding ZnT8A and associated results letters

Newsletter, Announcement or Script description of the rational for adding ZnT8:

Many years ago researchers found the three autoantibodies we test for in TEDDY (GAD, IAA, IA-2). Testing for these autoantibodies improves our ability to predict who will get type 1 diabetes (T1D). Sometime children develop diabetes without having these three autoantibodies. This led researchers to look for other autoantibodies that might indicate that the auto-immune process had started. Researchers have since discovered another autoantibody now called ZnT8. The ZnT8 autoantibody usually shows up once someone is already positive for another autoantibody. TEDDY has started testing those children who are autoantibody positive for the presence of ZnT8. We hope this information will help us learn more about howT1D develops.

Your results letter may look different from now on. If your child has tested positive for any of the three autoantibodies we have always tested for, you will also see ZnT8 test results added to your letter. Like the other results, ZnT8 results may be positive or negative for your child.

ADDED or ALTERNATE PARAGRAPH FOR WHEN THERE IS A LONG LAG BETWEEN RESULTS:
The ZnT8 results are sent to central lab for all TEDDY centers. Because these are sent after the usual autoantibody tests are run there may be a delay in getting the ZnT8 results. Our goal is to make sure that you get all results as soon as is possible. Though this may mean we give you two sets of results from a given visit. (We can work on this)

The risk for developing T1D is higher when autoantibodies are present. A positive result for ZnT8 is similar to being positive for the other autoantibodies. Being positive for two or more autoantibodies increases the risk of T1D more than being single autoantibody positive. The risk associated with having multiple autoantibodies is the same in children with and without a family history of diabetes. With multiple autoantibodies it is important to monitor blood sugars at home and by coming to TEDDY visits.

Scripts for communications or letters (really currently letters just adding ZnT8 where appropriate) If results are being given orally in-person or over the phone, they would mimic the content of these letters.

Letter Communication 1: AB- for GAD, IAA, IA-2 (ZnT8 not run)-AB- letter/communication
No Change

Letter/Communication 2: Subject is single ab+ but ZnT8 was run because other AB was positive (in this case ZnT8 would be negative). This is essentially the same single AB+ letter that has ZnT8 result line added.

Dear Participant,

The results of the TEDDY autoantibody testing for [Subject Name] drawn on [date] are:
GAD
IAA
IA-2

ZnT8

This is a screening test to determine if autoantibodies to the pancreas are present. This means your child is at increased risk, though it is important to realize that even though your child continues to be positive for one autoantibody, it does not mean your child will definitely develop diabetes. Only 1 out of 4 children positive for 1 autoantibody will develop diabetes by the age of 20.

Letter/Communication 3: For subjects where there is any combination of multiple AB+ including where ZnT8 was run and could be positive or negative. This is essentially the same letter as we currently use, just with ZnT8 result included.

Dear Participant,

The results of the TEDDY autoantibody testing for [Subject Name] drawn on [date] are:
GAD
IAA
IA-2
ZnT8

This is a screening test to determine if autoantibodies to the pancreas are present. Your child was found to be positive for two or more diabetes autoantibodies. Being positive for multiple autoantibodies may significantly increase the possibility that your child could develop diabetes during childhood. Although this doesn't mean your child will definitely develop diabetes it is important to follow your child closely. Therefore we recommend monitoring these autoantibodies every 3 months at TEDDY visits and testing your child's blood sugar at home.

Because your child is at higher risk, it is important for you to be aware of the early symptoms of diabetes which are:

Increased thirst	*Decreased appetite for solid foods*
Increased urination	*Bed wetting in a previously dry child*
Nausea	*Yeast infection with a rash (especially in diaper area)*
Vomiting (without diarrhea)	*Decreased energy*

If your child has two or more of the above symptoms please call your study nurse or physician.

QQ. Thyroid Staff Sheet

Why does TEDDY care about your thyroid?
TEDDY is interested in the autoimmune forms of thyroid disease because they share some of the same genetic risk factors as diabetes.
TEDDY is interested in autoimmune disorders that may impact the development of type 1 diabetes (such as celiac, which we started testing children for at 2 years of age.)

What is thyroid disease?
The main purpose of thyroid hormone is to run the body's metabolism. Hypothyroid is a condition in which the body lacks sufficient thyroid hormone. In hyperthyroid, the gland produces too much hormone. Depending upon the specific autoimmune attack, low or high thyroid can occur.

What causes it?
The most common cause of thyroid problems is autoimmunity. Medical treatments that remove all or part of the thyroid gland, or environmental factors such as radiation exposure can also cause hypothyroidism.

What are the symptoms?

Hypothyroid

- Fatigue
- Weakness
- Weight gain or difficulty losing weight
- Coarse, dry hair
- Dry, rough pale skin
- Hair loss
- Cold intolerance
- Muscle cramps and muscle aches
- Constipation
- Depression
- Irritability
- Memory loss
- Abnormal menstrual cycles

Hyperthyroid

- Weight Loss
- Excessive Sweating
- Hyperactivity
- Heat intolerance
- Diarrhea
- Insomnia
- Muscle weakness
- Deterioration in handwriting
- Eye pain or seeing double
- Abnormal menstrual cycle

How is it diagnosed?
The symptoms related to hypothyroidism are not very specific and tend to be subtle as they occur over time. Because of this, hypothyroidism is diagnosed by lab tests measuring Thyroid Stimulating Hormone (TSH) and thyroid hormone (T4) levels.

All TEDDY children that test positive for thyroid autoantibodies will also have TSH levels measured by the TEDDY core lab. Referrals for abnormal results will then be made, based on the combination of antibodies and hormone levels.

How is it treated?
Hypothyroidism is easily treated by taking a synthetic replacement hormone. In most cases, individuals respond quickly to treatment and symptoms disappear within a few months.

When left untreated, hypothyroidism can lead to more severe complications over time, however, there is no immediate emergency, and diagnosis and treatment can and should be done in the doctor's office.

RR. MODEL LETTER FOR REPORTING THYROID POSITIVE AUTOANTIBODY RESULTS (TPOA or ThGA) BUT TSH IS NORMAL

Parent Doe
123 Main Street
Anytown, WA 98123

Dear _____,

This is a follow-up letter to the telephone call we had about your child's thyroid autoantibody test results. At (CHILD"S NAME)'s last TEDDY Study visit on (DATE OF LAST CLINIC VISIT) we tested his/her blood for the thyroid peroxidase (TPOA) and thyroglobulin (ThGA) autoantibodies. Additionally, we test thyroid stimulating hormone (TSH) levels for children that test positive for autoantibodies. These tests are used to screen people for thyroid disease. Thyroid disease is an autoimmune disease caused when healthy thyroid cells are mistakenly attacked by the immune system. Your child's test results are listed below.

Test Name	Normal Level	Your Child's Results	Meaning
TPOA	≤ 1 U/mL		
ThGA	≤ 1 U/mL		
TSH	0.4 – 4 µIU/mL		

Your child tested positive for autoantibodies specific to thyroid disease. Your child's TSH levels were within normal. We recommend that your follow up with your child's physician and provide them a copy of these results. This is not urgent, and can be done at your child's next doctor's visit.

Your child's doctor will most likely add routine thyroid testing to your child's regular visits.

If you have any questions or concerns, please call us on our toll free number _____.

Your next TEDDY study visit is scheduled for _____(provide data and time). We look forward to seeing you then.

Thanks so much for your participation in this important study.

Sincerely yours,

Site PI

SS. MODEL LETTER FOR REPORTING THYROID POSITIVE AUTOANTIBODY RESULTS (TPOA or ThGA) AND TSH IS BORDERLINE

Parent Doe
123 Main Street
Anytown, WA 98123

Dear _____,

This is a follow-up letter to the telephone call we had about your child's thyroid autoantibody test results. At (CHILD"S NAME)'s last TEDDY Study visit on (DATE OF LAST CLINIC VISIT) we tested his/her blood for the thyroid peroxidase (TPOA) and thyroglobulin (ThGA) autoantibodies. Additionally, we test thyroid stimulating hormone (TSH) levels for children that test positive for autoantibodies. These tests are used to screen people for thyroid disease. Thyroid disease is an autoimmune disease caused when healthy thyroid cells are mistakenly attacked by the immune system. Your child's test results are listed below.

Test Name	Normal Level	Your Child's Results	Meaning
TPOA	$\leq$ 1 U/mL		
ThGA	$\leq$ 1 U/mL		
TSH	0.4 – 4 µIU/mL		

Your child tested positive for autoantibodies specific to thyroid disease and your child's TSH levels came back in the borderline range. We recommend that your follow up with your child's physician and provide them a copy of these results. While not urgent, we recommend following up with your child's doctor within the next month.

If you have any questions or concerns, please call us on our toll free number _____.

Your next TEDDY study visit is scheduled for _____(provide data and time). We look forward to seeing you then.

Thanks so much for your participation in this important study.

Sincerely yours,

Site PI

TT. MODEL LETTER FOR REPORTING FIRST-TIME POSITIVE AUTOANTIBODY RESULTS (TPOA or ThGA) BUT TSH IS VERY HIGH OR LOW

Parent Doe
123 Main Street
Anytown, WA 98123

Dear _____,

This is a follow-up letter to the telephone call we had about your child's thyroid autoantibody test results. At (CHILD"S NAME)'s last TEDDY Study visit on (DATE OF LAST CLINIC VISIT) we tested his/her blood for the thyroid peroxidase (TPOA) and thyroglobulin (ThGA) autoantibodies. Additionally, we test thyroid stimulating hormone (TSH) levels for children that test positive for autoantibodies. These tests are used to screen people for thyroid disease. Thyroid disease is an autoimmune disease caused when healthy thyroid cells are mistakenly attacked by the immune system. Your child's test results are listed below.

Test Name	Normal Level	Your Child's Results	Meaning
TPOA	$\leq$ 1 U/mL		
ThGA	$\leq$ 1 U/mL		
TSH	0.4 – 4 µIU/mL		

Your child tested positive for autoantibodies specific to thyroid disease. Also, your child's TSH levels came back outside normal range. Because of these results, we recommend following up with your child's doctor as soon as possible. Please provide your doctor with a copy of these results.

If you have any questions or concerns, please call us on our toll free number _____.

Your next TEDDY study visit is scheduled for _____(provide data and time). We look forward to seeing you then.

Thanks so much for your participation in this important study.

Sincerely yours,

Site PI

UU. MODEL THYROID AUTOANTIBODY NEGATIVE LETTER

Date

Address

Dear (Parent Contact Name),

At (CHILD'S NAME)'s last TEDDY Study visit on (DATE OF LAST CLINIC VISIT) we tested his/her blood for the thyroid peroxidase (TPOA) and thyroglobulin (ThGA) autoantibodies. The thyroid peroxidase and thyroglobulin autoantibodies are used to screen people for thyroid disease. Thyroid disease is an autoimmune disease caused when healthy thyroid cells are mistakenly attacked by the immune system.

We are writing to tell you that the results of the thyroid autoantibody tests were negative.

We will test your child again for this autoantibody at the age of 14 in the TEDDY Study. As always, all tests are free of charge and your participation in TEDDY is voluntary.

If you have any questions about these test results or the TEDDY study, please call us at (XXX) XXX –XXXX. We will contact you soon about your next appointment. Please be sure let us know if you have a change of address or phone number.

Thank you for taking part in the TEDDY study. We look forward to seeing you at your next clinic visit.

Sincerely,

Site PI

VV. MODEL POSITIVE THYROID AUTOANTIBODY LETTER FOR PHYSICIAN

Doctor
123 Main Street
Anytown, WA 98123

Dear Dr._____,

Your patient, (CHILD) has been a research participant in the NIH funded TEDDY study (The Environmental Determinants of Diabetes in the Young) for (LENGTH OF TIME) after meeting inclusion criteria of increased genetic risk for developing type 1 diabetes due to HLA genotyping. We have been testing (CHILD'S NAME) for the presence of diabetes autoantibodies (GADA, IA-2A or IAA) as part of our protocol.

We have also tested (CHILD'S NAME) for the presence of thyroid peroxidase (TPOA) and thyroglobulin (ThGA) autoantibodies at age (AGE) as part of our protocol. TSH is additionally measured if either of these results is positive. (CHILD) has tested positive as follows:

Name of Test	Normal Level	Child's Results
TPOA	$\leq$ 1 U/mL	
ThGA	$\leq$ 1 U/mL	
TSH	0.4 – 4 µIU/mL	

We have encouraged the child's parents to contact their primary care physician for follow-up as needed. (CHILD) parents have requested we send you this information. We usually advise TEDDY participants to keep experimental research findings out of their medical records for confidentiality reasons.

If I can be of any assistance in the future regarding these results, please do not hesitate to call (xxxx) or email (xxx) me anytime.

Sincerely yours,

Site PI

WW. TEDDY RESULTS REPORT – GIVEN TO FAMILY AT 15 YEAR VISIT (English version)

DATE OF LAST VISIT

Dear (NAME OF TEDDY PARTICIPANT)

Since you were three months old, you have been part of the largest study of type 1 diabetes in the world. You are one of the 8667 children who are a part of The Environmental Determinants of Diabetes in the Young (TEDDY) study. TEDDY is an international study funded primarily by the National Institutes of Health to investigate factors that may trigger or protect against type 1 diabetes. We asked you to be in TEDDY because you have an increased risk for type 1 diabetes. TEDDY was designed to follow children in the United States, Sweden, Finland, and Germany from birth to their 15th birthday.

You and your parents have made a great contribution to science with your participation for the first 15 years of your life. We are very grateful that you took part in TEDDY, and we want to share with you as much information as possible.

The table below lists your most recent results. A more detailed interpretation of each follows the table. We think these things are important for you to know. You should consider sharing these results with your health care provider.

	Autoantibody Results For:		
	1. Type 1 Diabetes Islet Autoantibodies	2. Celiac Disease tTG Autoantibody	3.Autoimmune Thyroid Disease TPO and TG Autoantibodies
	a. Always Negative b. Previously Islet Autoantibody Positive, Most recently Negative c. Most recently Single Islet Autoantibody Positive d. Ever Multiple Islet Autoantibodies Positive	a. Always Negative b. Previously tTGA Positive, most recently Negative c. Most recently tTGA Positive d. Diagnosed with Celiac Disease while in TEDDY	a. Always Negative b. Most recently Autoantibody Positive with Normal TSH c. Most recently Autoantibody Positive with Abnormal TSH d. Diagnosed with Autoimmune Thyroid Disease while in TEDDY
Date of Test			

1. TYPE 1 DIABETES TESTING

At every visit, we tested you for autoantibodies that are specific to type 1 diabetes. These autoantibodies indicate an ongoing immune system process in the pancreas. We have measured four islet autoantibodies: IAA, GADA, IA-2A and ZnT8A. (The full autoantibody names are given at end of this report.) Your risk of type 1 diabetes depends on how many of these islet autoantibodies you have tested positive for while you were in TEDDY.
Your most recent results are:

1a. Always Negative:

In 15 years, you have not developed any islet autoantibodies, making it less likely that you will develop type 1 diabetes. The possibility of developing islet autoantibodies is highest in the early childhood (under 5 years of age). Islet autoantibodies do develop after 15 years of age, but less often than in childhood. We recommend that you be familiar with the symptoms of type 1 diabetes and contact your health center if you start experiencing any of them.

1b. Previously Positive:
While your type 1 diabetes islet autoantibodies are currently negative, you have had positive results in the past. Your risk for type 1 diabetes may be more than someone who has always been negative. The possibility of developing islet autoantibodies is highest in early childhood (under 5 years of age). Islet autoantibodies do develop after 15 years of age, but less often than in childhood. We do recommend that you be familiar with the symptoms of type 1 diabetes and contact your health center if you start experiencing any of them.

1c. Single Positive:
A single autoantibody increases your type 1 diabetes risk. Within 10 years of developing a single islet autoantibody, approximately 15% (15 out of 100) of individuals will develop type 1 diabetes. The increased risk continues beyond 10 years, however, most people with only one islet autoantibody will not go on to get type 1 diabetes. In addition to being familiar with the symptoms of type 1 diabetes, we recommend sharing these results with your health care provider.

1d. Multiple Positive:
Two or more islet autoantibodies are highly predictive of type 1 diabetes, but time to onset varies from months to years. Within 10 years of developing multiple islet autoantibodies, approximately 70% (70 out of 100) of individuals will develop type 1 diabetes. The increased risk continues beyond 10 years.

These results only tell us about your risk for type 1 diabetes. They do not tell us about your risk for other types of diabetes.

It is important that you are familiar with the symptoms of type 1 diabetes:

Symptoms include:
- Excessive thirst
- No energy (tiredness)
- Increased urination
- Weight loss

If you observe any of these symptoms, it is important to seek immediate health care assistance. Early treatment of type 1 diabetes may prevent a severe illness, called **diabetic ketoacidosis**.

2. CELIAC DISEASE TESTING

Every year starting at 2 years old, you were screened for tissue transglutaminase autoantibodies (tTGA). Celiac disease is an autoimmune disease. It causes an immune reaction in the intestine when gluten is consumed. Gluten is a protein found in wheat, barley and rye. Celiac disease causes damage to the small intestine resulting in poor absorption of nutrients. Common symptoms of celiac disease may include gastrointestinal complaints, such as chronic constipation or frequent loose stools. These symptoms may be associated with other illnesses. Your most recent results are:

2a. Always Negative:
Your tTGA results have always been negative. We do not recommend any additional follow-up at this time other than usual care.

2b. Previously Positive:
While your tTGA result is currently negative, you have had positive results in the past. We recommend that your health care provider retests your tTGA every few years in case celiac disease develops in the future.

2c. Most Recently Positive:
Your most recent tTGA result was positive. Having a positive test does not necessarily mean that celiac disease is present, but it does increase the risk of having it. We recommend that you discuss these results with your health care provider, as you may need follow up with a gastroenterologist.

2d. Diagnosed with Celiac Disease
Our records show that you were diagnosed with celiac disease during the time you participated in the TEDDY Study. Please continue to follow your health care provider's recommendations.

3. AUTOIMMUNE THYROID TESTING

Thyroid autoantibodies have been tested in TEDDY since 2016. We tested you twice for thyroid autoantibodies, once between ages 8 and 12 and again at 14 years.
Your most recent results are:

3a. Always Negative:

Your results have been negative for thyroid autoantibodies, so we do not recommend any follow-up at this time. However, if you begin to see the symptoms listed below contact your health care provider.

3b. Most Recently Positive:
Since your results were positive, we also tested Thyroid Stimulating Hormone (TSH) which gives us an indication of how well your thyroid is performing.

With Normal TSH: While you tested positive for thyroid autoantibodies, your TSH level was normal. We recommend that you continue to follow up with your health care provider. They may regularly repeat TSH testing. You should be aware of the symptoms listed below. In case of symptoms, you should contact your health care provider.

It is recommended for females with known positive thyroid autoantibodies to test their thyroid function before pregnancy, as normal thyroid function is important during pregnancy.

3c. Most Recently Positive:
Since your results were positive, we also tested Thyroid Stimulating Hormone (TSH) which gives us an indication of how well your thyroid is performing.

With Abnormal TSH: In addition to being positive for thyroid autoantibodies, your TSH level was abnormal. We recommend that your health care provider refer you to an endocrinologist for a full evaluation.

It is recommended for females with known positive thyroid autoantibodies to test their thyroid function before pregnancy, as normal thyroid function is important during pregnancy.

3d. Diagnosed with Autoimmune Thyroid Disease
Our records show that you were diagnosed with thyroid disease during the time you participated in the TEDDY Study. Please continue to follow your health care provider's recommendations.

Symptoms of hypothyroidism (low thyroid) can be subtle and may include the following. These symptoms may also be associated with other illnesses.

- Enlargement of the thyroid gland (goiter)
- Tiredness
- Impaired school performance
- Poor growth
- Dry skin
- Constipation
- Cold intolerance
- Menstrual irregularities
- Hair loss

Symptoms of hyperthyroidism (excessive thyroid):

- Enlargement of the thyroid gland (goiter)
- Elevated heart rate
- Trouble sleeping
- Diarrhea
- Weight loss
- Increased appetite
- Heat intolerance
- Menstrual irregularities

With your participation in TEDDY, we understand better how the immune system contributes to the development of type 1 diabetes and other autoimmune diseases. TEDDY is the starting point to develop novel approaches to delay or prevent type 1 diabetes, celiac disease and thyroid autoimmunity.
We could not have done it without you.

THANK YOU!

Abbreviations:
IAA = insulin autoantibody; GADA = glutamic acid decarboxylase autoantibody; IA-2A = islet antigen-2 autoantibody; ZnT8A = zinc transporter 8 autoantibody

XX. TEDDY RESULTS REPORT – GIVEN TO FAMILY AT 15 YEAR VISIT (Finnish version)

15-VUOTISKÄYNNIN PÄIVÄMÄÄRÄ

Hyvä (TUTKITTAVAN NIMI)

Kolmen kuukauden iästä saakka olet ollut mukana maailman laajimmassa tyypin 1 diabetes (T1D) –tutkimuksessa. Olet yksi 8667:stä lapsesta, joka on ollut mukana tutkimuksessa "Ympäristötekijöiden osuus tyypin 1 diabeteksen kehittymisessä" (The Environmental Determinants of Diabetes in the Young, TEDDY). TEDDY on Yhdysvaltain terveysviraston (National Institute of Health, NIH) perustama kansainvälinen tutkimus, jossa selvitetään tekijöitä, jotka voivat laukaista diabeteksen tai suojata sen kehittymiseltä. Olet osallistunut TEDDY-tutkimukseen, koska sinulla on kohonnut perinnöllinen riski tyypin 1 diabetekseen. TEDDY-tutkimuksessa lapsia on seurattu Yhdysvalloissa, Ruotsissa, Suomessa ja Saksassa syntymästä 15 vuoden ikään asti.

Sinä ja vanhempasi olette olleet suureksi avuksi tieteelle osallistumalla TEDDY-käynneille 15 vuoden ajan. Olemme hyvin kiitollisia siitä, että olet ollut mukana TEDDY-tutkimuksessa ja haluamme tässä jakaa sinulle mahdollisimman paljon tietoa.

Alla olevassa taulukossa on listattuna viimeisimmät tuloksesi. Tarkemman kuvauksen siitä, mitä ne tarkoittavat, löytyy taulukon jälkeen. On tärkeää, että sinä tiedät näistä ja jaat tiedot mahdollisesti myös omalle terveyskeskuksellesi.

	Autovasta-ainetulokset:		
	1. Tyypin 1 Diabetes autovasta-aineet	2. Keliakia tTG autovasta-aine	3. Kilpirauhasen autoimmuunisairaus TPO ja TG autovasta-aineet
	a. Aina negatiivinen b. Aiemmin autovasta-ainepositiivinen, viimeisin tulos negatiivinen c. Viimeisin tulos yhdelle autovasta-aineelle positiivinen d. On ollut tai on monelle autovasta-aineelle positiivinen	a. Aina negatiivinen b. Aiemmin tTGA positiivinen, viimeisin tulos negatiivinen c. Viimeisin tulos tTGA positiivinen d. Keliakiadiagnoosi TEDDY-tutkimuksen aikana	a. Aina negatiivinen b. Viimeisin tulos autovasta-ainepositiivinen ja normaali TSH c. Viimeisin tulos autovasta-ainepositiivinen ja epänormaali TSH d. Kilpirauhasen autoimmuunisairausdiagnoosi TEDDY-tutkimuksen aikana
Testauspäivämäärä:			

1. <u>TYYPIN 1 DIABETESTESTAUS</u>

Joka käynnillä olemme tutkineet verinäytteestäsi autovasta-aineita, jotka ovat ominaisia tyypin 1 diabetekselle. Näiden autovasta-aineiden ilmaantuminen viittaa käynnissä olevaan immuunijärjestelmän muutokseen haimassa. Olemme mitanneet neljää autovasta-ainetta: IAA,

GADA, IA2A ja ZnT8A (näiden autovasta-aineiden koko nimet ovat raportin lopussa). Riskisi sairastua tyypin 1 diabetekseen riippuu siitä, kuinka monta autovasta-ainetta sinulla on TEDDY-tutkimuksessa havaittu.
Sinun viimeisimmät tuloksesi ovat:

1a. Aina negatiiviset:
Sinulla ei ole 15 vuoden aikana ollut yhtään autovasta-aineita. Ei siis ole todennäköistä, että sairastuisit tyypin 1 diabetekseen. Todennäköisyys autovasta-aineiden kehittymiselle on korkeimmillaan varhaislapsuudessa (alle viiden vuoden iässä). Autovasta-aineita voi muodostua myös 15 vuoden iän jälkeen, mutta harvemmin kuin lapsuudessa. Suosittelemme, että perehdyt tyypin 1 diabeteksen oireisiin ja otat yhteyttä terveyskeskukseesi, mikäli tunnistat itsessäsi niitä.

1b. Aiemmin positiivinen:
Vaikka sinun tyypin 1 diabeteksen autovasta-ainetuloksesi ovat tällä hetkellä negatiiviset, sinulla on aiemmin ollut positiivisia tuloksia. Riskisi sairastua tyypin 1 diabetekseen saattaa olla suurempi kuin henkilön, joka on aina ollut autovasta-ainenegatiivinen. Todennäköisyys autovasta-aineiden kehittymiselle on korkeimmillaan varhaislapsuudessa (alle viiden vuoden iässä). Autovasta-aineita voi muodostua myös 15 vuoden iän jälkeen, mutta harvemmin kuin lapsuudessa. Suosittelemme, että perehdyt tyypin 1 diabeteksen oireisiin ja otat yhteyttä terveyskeskukseesi, mikäli tunnistat itsessäsi niitä.

1c. Yksi positiivinen autovasta-aine:
Yksi autovasta-aine lisää tyypin 1 diabetesriskiäsi. Kymmenen vuoden kuluessa yhden autovasta-aineen ilmaantumisesta noin 15 % (viisitoista sadasta) sairastuu tyypin 1 diabetekseen. Kohonnut riski jatkuu vielä 10 vuoden jälkeen, mutta suurin osa henkilöistä, joilla on vain yksi autovasta-aine ei sairastu tyypin 1 diabetekseen. Suosittelemme, että perehdyt tyypin 1 diabeteksen oireisiin ja kerrot tästä tuloksesta asioidessasi terveyskeskuksessa. Tarjoamme sinulle myös mahdollisuutta jatkaa seurantaa DIPP-tutkimuksessa.

1d. Monta positiivista autovasta-ainetta:
Kaksi tai useampi autovasta-aine ennustaa hyvin tyypin 1 diabeteksen ilmaantumista, mutta sairastumisen hetki vaihtelee kuukausista vuosiin. Kymmenen vuoden kuluessa useamman autovasta-aineen ilmaantumisesta noin 70 % (seitsemänkymmentä sadasta) tulee sairastumaan tyypin 1 diabetekseen. Kohonnut riski jatkuu vielä 10 vuoden jälkeenkin. Suosittelemme, että perehdyt tyypin 1 diabeteksen oireisiin ja kerrot tästä tuloksesta asioidessasi terveyskeskuksessa. Tarjoamme sinulle mahdollisuutta jatkaa seurantaa DIPP-tutkimuksessa.

Nämä tulokset kertovat vain riskistäsi sairastua tyypin 1 diabetekseen. Ne eivät kerro riskistäsi sairastua muihin diabetestyyppeihin.

On tärkeää, että perehdyt tyypin 1 diabeteksen oireisiin.
Oireita ovat:
- Voimakas janontunne
- Vetämätön olo (väsymys)
- Tiheävirtsaisuus
- Laihtuminen

On tärkeää, että otat välittömästi yhteyttä terveyskeskukseesi, mikäli tunnistat itsessäsi mitään näistä oireista. Diabeteksen varhainen hoito voi estää **diabeettisen ketoasidoosin** syntymisen, joka on vakava sairaustila.

2. KELIAKIATESTAUS

Joka vuosi kahden vuoden iästä alkaen olemme tutkineet verinäytteestäsi kudostransglutaminaasi-autovasta-aineita (tTGA). Keliakia on autoimmuunisairaus. Se aiheuttaa suolistossa immuunireaktion, kun ruokavalio sisältää gluteenia. Gluteeni on proteiini, jota on vehnässä, ohrassa ja rukiissa. Keliakia vaurioittaa ohutsuolta ja johtaa ravintoaineiden huonon imeytymiseen. Tyypilliset keliakiaoireet voivat olla maha-suolikanavan vaivoja, kuten kroonista ummetusta tai toistuvasti löysiä ulosteita. Nämä oireet saattavat liittyä myös muihin sairauksiin.
Sinun viimeisimmät tuloksesi ovat:

2a. Aina negatiivinen:
Sinun tTGA tuloksesi ovat aina olleet negatiivisia. Emme suosittele sinulle mitään jatkoseurantaa tällä hetkellä.

2b. Aiemmin positiivinen:
Vaikka sinun tTGA-tuloksesi on tällä hetkellä negatiivinen, sinulla on aiemmin ollut positiivisia tuloksia. Suosittelemme tTGA-määritystä muutaman vuoden välein, jotta keliakian mahdollinen puhkeaminen havaitaan.

2c. Viimeisin tulos positiivinen:
Sinun viimeisin tTGA-tuloksesi oli positiivinen. Positiivinen testitulos ei välttämättä tarkoita, että sinulla olisi keliakia, mutta se lisää riskiäsi sairastua siihen. Suosittelemme, että kerrot tästä tuloksesta terveyskeskuksessasi. Saattaa olla, että tarvitset jatkoseurantaa sisätautien poliklinikalla.

2d. Keliakiadiagnoosi
Tutkimusaineistomme mukaan sinulla on diagnosoitu keliakia TEDDY-tutkimuksen aikana. Suosittelemme, että jatkat keliakian seurantaa omalla poliklinikallasi.

3. KILPIRAUHASTESTAUS

Kilpirauhasen autovasta-aineita on tutkittu TEDDY:ssä vuodesta 2016 lähtien. Olemme tutkineet sinulta kilpirauhasen autovasta-aineita kahdesti; ensimmäisen kerran 8-12 vuoden iässä ja uudelleen 14 vuoden iässä.
Sinun viimeisimmät tuloksesi ovat:

3a. Aina negatiivinen:
Sinun kilpirauhasen autovasta-ainetulokset ovat olleet negatiivisia. Emme suosittele sinulle tällä hetkellä mitään jatkoseurantaa. Mikäli sinulla ilmenee alla listattuja kilpirauhassairauden oireita, ota yhteyttä terveyskeskukseesi.

3b. Viimeisin tulos positiivinen:
Koska tuloksesi olivat positiivisia, tutkimme myös tyreotropiinitasosi (TSH-tasosi), joka kertoo sinun kilpirauhasesi toiminnasta.
Normaali TSH: Vaikka sinulla oli kilpirauhasen autovasta-aineita, oli TSH-tasosi normaali. Suosittelemme, että kerrot näistä tuloksesta terveyskeskuksessasi, jossa sinun TSH-tasosi voidaan

mitata säännöllisesti. Kehotamme sinua perehtymään alla listatuttuihin oireisiin. Mikäli sinulla ilmenee oireita, ota yhteyttä terveyskeskukseesi.

On suositeltavaa, että naiset, joilla on kilpirauhasen autovasta-aineita, testauttaisivat kilpirauhasen toiminnan ennen raskauden suunnittelua, sillä normaali kilpirauhasen toiminta on tärkeää raskauden aikana.

3c. Viimeisin tulos positiivinen:
Koska tuloksesi olivat positiivisia, tutkimme myös tyreotropiinitasosi (TSH-tasosi), joka kertoo sinun kilpirauhasesi toiminnasta.
Epänormaali TSH: Sen lisäksi, että kilpirauhasen autovasta-ainetestituloksesi oli positiivinen, myös TSH-tuloksesi oli epänormaali. Tämän vuoksi sinusta on tehty lähete lastenendokrinologian poliklinikalle jatkoseurannan suunnittelua ja hoidon aloitusta varten.

On suositeltavaa, että naiset, joilla on kilpirauhasen autovasta-aineita, testauttaisivat kilpirauhasen toiminnan ennen raskauden suunnittelua, sillä normaali kilpirauhasen toiminta on tärkeää raskauden aikana.

3d. Kilpirauhasen autoimmuunisairausdiagnoosi
Sinulla on diagnosoitu TEDDY-tutkimuksen aikana kilpirauhasen autoimmuunisairaus. Suosittelemme, että käyt edelleen lääkärin jatkoseurannassa.

Kilpirauhasen vajatoiminnan (hypotyreoosi) oireet voivat olla hyvin lieviä ja voivat olla seuraavia. Nämä oireet saattavat liittyä myös muihin sairauksiin.
- Kilpirauhasen suurentuminen (struuma)
- Väsymys
- Heikentynyt suoriutuminen koulussa
- Hidas kasvu
- Kuiva iho
- Ummetus
- Kylmänarkuus
- Epäsäännölliset kuukautiset
- Hiustenlähtö

Kilpirauhasen liikatoiminnan (hypertyreoosi) oireet ovat:
- Kilpirauhasen suurentuminen (struuma)
- Kohonnut syke
- Univaikeudet
- Ripuli
- Laihtuminen
- Ruokahalun kasvaminen
- Heikentynyt lämmönsieto
- Epäsäännölliset kuukautiset

Osallistumisesi TEDDY-tutkimukseen on lisännyt ymmärrystämme siitä, miten immuunijärjestelmä vaikuttaa tyypin 1 diabeteksen ja muiden autoimmuunisairauksien syntyyn. TEDDY on lähtökohta uusien toimintatapojen kehittämiselle, jotta voimme hidastaa tai estää tyypin 1 diabetesta, keliakiaa ja kilpirauhasen autoimmuunisairauksia. Emme olisi pystyneet tähän ilman sinua.

KIITOS!

Lyhenteet:
IAA = insuliinia tunnistava autovasta-aine; GADA = glutamaattidekarboksylaasientsyymiä tunnistava autovasta-aine; IA-2A = ja insulinooma-antigeeni-2:ta tunnistava autovasta-aine; ZnT8A = sinkkitransportteri 8 -molekyyliä tunnistava autovasta-aine

YY. TEDDY RESULTS REPORT – GIVEN TO FAMILY AT 15 YEAR VISIT (Swedish version)

Kära: **Datum:**

Sedan du var tre månader gammal har du varit med i världens största forskningsstudie om autoimmun (typ 1) diabetes. Du är ett av de 8667 barn som deltar i The Environmental Determinants of Diabetes in the Young (TEDDY). TEDDY är en internationell studie som finansieras av National Institutes of Health för att ta reda på vilka faktorer som triggar eller skyddar mot typ 1-diabetes. Vi tillfrågade dig att delta i TEDDY på grund av att du har en förhöjd ärftlig risk för typ 1-diabetes. TEDDY har följt barn från USA, Sverige, Finland och Tyskland från födseln till deras 15 års dag.

Du och dina föräldrar har bidragit till forskningen genom att besöka och lämna prover till TEDDY flera gånger om året under dina första 15 år. Vi är mycket tacksamma för ditt deltagande i TEDDY och vi vill dela med oss så mycket vi kan av den information vi har.

I tabellen nedan visas de senaste resultaten. En mer detaljerad information finns under tabellen. Vi tror att detta är viktigt för dig att känna till och att du delar med dig av informationen om du eventuellt behöver söka sjukvård.

	Autoantikroppsresultat för:		
	1. Typ 1-diabetes autoantikroppar	2. Celiaki tTG antikroppar (tTGA)	3.Autoimmun Tyreoidit/Sköldkörtelinflammation TPO och TG autoantikroppar
	a. Alltid negativ b. Tidigare autoantikroppspositiv för en autoantikropp, numera negativ c. Nu positiv för en autoantikropp d. Nu eller tidigare positiv för flera autoantikroppar	a. Alltid negativ b. Tidigare tTGA positiv, numera negativ c. Nu positiv för tTGA d. Diagnostiserad med celiaki när du var med i TEDDY	a. Alltid negativ b. Nu autoantikroppspositivt resultat med normalt TSH c. Nu autoantikroppspositivt resultat med onormalt TSH d. Diagnostiserad med autoimmun tyreoidit/sköldkörtelinflammation när du var med i TEDDY
Datum för provtagning:			

1. TYP 1-DIABETES PROVTAGNING

Vid varje besök testade vi dig för autoantikroppar som är specifika för typ 1-diabetes. Dessa autoantikroppar visar att immunsystemet håller på att angripa betacellerna i bukspottskörteln. Vi har mätt fyra olika autoantikroppar: IAA, GADA, IA-2A och ZnT8A. (Du finner autoantikropparnas hela namn längst ner i brevet). Din risk för typ 1-diabetes beror på hur många autoantikroppar du har haft under tiden du deltagit i TEDDY.
Dina senaste resultat är:

1a. Alltid negativa:
Eftersom du inte har haft autoantikroppar finns det just nu inget som talar för att du kommer att få typ 1-diabetes. Risken att utveckla autoantikroppar är störst i den tidiga barndomen (under 5 års ålder). Autoantikroppar kan utvecklas efter 15 års ålder men det är inte lika vanligt som i barndomen. Vi rekommenderar att du känner till symtomen för typ 1-diabetes och söker vård om du upplever några av dem.

1b. Tidigare positiv för en autoantikropp:
Just nu visar inte ditt blodprov på några autoantikroppar men du har haft positiva resultat tidigare. Din risk för typ 1-diabetes är troligen något högre jämfört med någon som alltid varit negativ. Risken att utveckla autoantikroppar är störst i den tidiga barndomen (under 5 års ålder). Autoantikroppar kan utvecklas efter 15 års ålder men det är inte lika vanligt som i barndomen. Vi rekommenderar att du känner till symtomen för typ 1-diabetes och söker vård om du upplever några av dem.

1c. En positiv autoantikropp:
En autoantikropp ökar din risk för typ 1-diabetes. Det innebär att din risk för typ 1-diabetes är 15% (15 av 100) inom 10 år. Den ökade risken kvarstår efter 10 år, men de flesta personer som endast har en autoantikropp kommer förmodligen inte att få typ 1-diabetes. Vi rekommenderar att du känner till symtomen för typ 1-diabetes och söker vård om du upplever några av dem.

1d. Flera positiva autoantikroppar:
Två eller flera autoantikroppar innebär en hög risk för typ 1-diabetes men tiden till att drabbas av sjukdomen varierar mellan några veckor till flera år. Totalt drabbas 70% (70 av 100) av de med flera autoantikroppar av typ 1-diabetes inom 10 år. Den ökade risken kvarstår efter 10 år. Vi rekommenderar att du känner till symtomen för typ 1-diabetes och söker vård om du upplever några av dem.

Ovanstående resultat visar vilken risk du har för typ 1-diabetes. Det säger ingenting om dina risker för att insjukna i andra former av diabetes.

Det är viktigt att du känner till symtomen för typ 1-diabetes:

Symtomen är:
- Ökad törst
- Ingen energi (trötthet)
- Stora urinmängder
- Viktminskning

Om du observerar några av dessa symtom är det viktigt att söka sjukvård omedelbart. Tidig upptäckt av typ 1-diabetes kan förhindra **ketoacidos** som är ett allvarligt tillstånd eftersom blodet blir surt.

2. CELIAKI PROVTAGNING

Varje år med början när du var 2 år har vi tagit prov för att se om du utvecklat en autoantikropp som kallas för vävnads transglutaminas antikroppar (tTGA). Celiaki är en autoimmun sjukdom som drabbar tunntarmens slemhinna orsakat av födoämnet gluten. Gluten är ett protein som finns i vete, korn och råg. Celiaki orsakar en skada i tarmen som gör att man har svårare att ta upp näring. Vanliga symtom på celiaki är obehag från magtarmkanalen som till exempel magont, förstoppning och diarré. Dessa symtom kan också vara tecken på andra sjukdomar.
Dina senaste resultat är:

2a. Alltid negativa:
Dina tTGA resultat har alltid varit negativa. Vi rekommenderar inte någon uppföljning i nuläget.

2b. Tidigare positiva resultat:
Dina tTGA resultat är just nu negativa men du har haft positiva värden tidigare.
Vi rekommenderar att du testar dig för tTGA när du upplever obehag från magtarmkanalen. Detta görs lämpligast på din vårdcentral.

2c. Positiva resultat:
Ditt senaste tTGA värde var positivt. Positivt testresultat behöver inte innebära att du har celiaki men det ökar risken för att få celiaki. Vi rekommenderar att du diskuterar detta med läkare på din vårdcentral.

2d. Diagnostiserad med celiaki:
Vår dokumentation visar att du har diagnostiserats med celiaki under de år du deltagit i TEDDY studien. Vi rekommenderar att fortsätta uppföljningen hos dietist och barnläkare tills du fyller 18 år. Därefter kommer du att remitteras till din vårdcentral för fortsatt uppföljning.

3. PROVTAGNING FÖR TYREODIT/SKÖLDKÖRTELINFLAMMATION

Autoantikroppar för tyreoidit (sköldkörtelinflammation) har analyserats i TEDDY sedan 2016. Vi har testat dig två gånger. Första gången var du 8–12 år gammal och sedan testade vi dig igen vid 14 års ålder.
Dina senaste resultat är:

3a. Alltid negativa:
Dina resultat för tyreoidea (sköldkörtel) autoantikroppar har alltid varit negativa så vi rekommenderar inte någon uppföljning i nuläget. Däremot, om du upplever några av symtomen vi nämner nedan bör du ta kontakt med sjukvården.

3b. Positiva resultat:
Eftersom dina resultat är positiva, har vi även analyserat ditt blod för Tyreoidea Stimulerande Hormon (TSH) vilket ger en indikation på hur din sköldkörtel fungerar.

Normalt TSH: När du testades positivt för tyreoidea autoantikroppar var ditt TSH normalt. Du bör vara uppmärksam på symtomen som nämns nedan. Vid symtom bör du kontakta sjukvården.

Kvinnor som planerar för en graviditet med positiva tyreoidea autoantikroppar rekommenderas att testa sin sköldkörtelfunktion. Det är viktigt att sköldkörteln fungerar som den ska under en graviditet.

3c. Positiva resultat:
Eftersom dina resultat är positiva, har vi även analyserat ditt blod för Tyreoidea Stimulerande Hormon (TSH) vilket ger en indikation på hur din sköldkörtel fungerar.

Onormalt TSH: När du testades positivt för tyreoidea autoantikroppar var ditt TSH onormalt. Vi har sedan tidigare remitterat dig till barnkliniken och uppföljning sker där.

Kvinnor som planerar för en graviditet med positiva tyreoidea autoantikroppar rekommenderas att testa sin sköldkörtelfunktion. Det är viktigt att sköldkörteln fungerar som den ska under en graviditet.

3d. Diagnostiserad med autoimmun tyreoidit (sköldkörtelinflammation)
Vår dokumentation visar att du är diagnostiserad med autoimmun tyreoidit (sköldkörtelinflammation) under de åren du deltagit i TEDDY studien. Vi rekommenderar att du fortsätter uppföljningen på barnkliniken för att få den bästa vården.

Symtomen kan vara diffusa och kan även vara tecken på andra sjukdomar.
Symtom för nedsatt sköldkörtelfunktion:

- Förstorad sköldkörtel
- Trötthet
- Försämrat eller dåligt minne
- Försämrad tillväxt
- Torr, grov och blek hy
- Förstoppning
- Frusenhet
- Onormal menstruationscykel

- Håravfall

Symtom för ökad sköldkörtelfunktion:

- Förstorad sköldkörtel
- Hjärtklappning
- Sömnsvårigheter
- Diarré
- Viktnedgång
- Ökad aptit
- Svettningar och värmekänsla
- Onormal menstruationscykel

Genom ditt deltagande i TEDDY, förstår vi bättre hur immunsystemet styr utvecklingen av typ 1-diabetes och andra autoimmuna sjukdomar. TEDDY har blivit startpunkten för att utveckla nya metoder och behandlingar för att skjuta upp eller förhindra typ 1-diabetes, celiaki och autoimmun tyreoidit.
Vi hade inte kunna göra det här utan dig och din familj.

TACK!

Förkortningar:
IAA = insulin autoantikropp; GADA = glutaminsyredekarboxylas autoantikropp; IA-2A = Islet antigen-2 autoantikropp; ZnT8A = zinktransportör 8 autoantikropp

ZZ. TEDDY RESULTS REPORT – GIVEN TO FAMILY AT 15 YEAR VISIT (German version)

Liebe(r)

seit Du drei Monate alt bist, nimmst Du an der weltweit größten Studie zu Typ-1-Diabetes (T1D) teil. Du bist eins von 8667 Kindern, das Teil der TEDDY-Studie (The Environmental Determinants of Diabetes in the Young) ist. TEDDY ist eine internationale Studie, die hauptsächlich von der nationalen Gesundheitsbehörde (NIH) in den USA gefördert wird. Ihr Ziel ist es, Faktoren zu aufzudecken, die die Entwicklung von Typ-1- Diabetes fördern oder davor schützen können. . In der TEDDY-Studie werden Kinder aus den USA, Schweden Finnland und Deutschland von Geburt bis zu ihrem 15. Geburtstag regelmäßig untersucht.

Zu Beginn der Studie wurde festgestellt, dass Du ein erhöhtes Risiko für Typ-1-Diabetes hast. Daher haben wir Dir und Deiner Familie empfohlen, an TEDDY teilzunehmen.
Durch Deine regelmäßigen Untersuchungen über die letzten 15 Jahre, haben Du und Deine Eltern einen großartigen Beitrag zur Wissenschaft geleistet. Wir sind sehr dankbar, dass Du an TEDDY teilgenommen hast. Deshalb möchten wir Dir zum Abschluss so viele Informationen wie möglich mit auf den Weg geben.

Die folgende Tabelle beinhaltet alle Ergebnisse der letzten Autoantikörper-Untersuchungen mit jeweils einer genaueren Erklärung.
Wir glauben, dass diese Informationen sehr wichtig für Dich sind und empfehlen, diese auch Deinem Arzt vorzulegen.

	Autoantikörper Ergebnisse für:		
	1. Typ-1-Diabetes Autoantikörper	2. Zöliakie-Autoantikörper	3. Schilddrüsen-Autoantikörper
	a. immer negativ b. früher Diabetes-Autoantikörper positiv, aktuell negativ c. aktuell positiv für einen Diabetes-Autoantikörper d. aktuell oder jemals positiv für 2 oder mehr Diabetes-Autoantikörper	a. immer negativ b. früher Zöliakie-Autoantikörper positiv, aktuell negativ c. aktuell Zöliakie-Autoantikörper positiv d. Diagnostizierte Zöliakie während TEDDY	a. immer negativ b. aktuell Schilddrüsen-Autoantikörper positiv mit normalem TSH-Spiegel c. aktuell Schilddrüsen-Autoantikörper positiv mit auffälligen TSH-Spiegel d. Diagnostizierte Schilddrüsenerkrankung während TEDDY
Datum der letzten Untersuchung			

Version 02-2020 Seite **1** of **7**

1. TYP-1-DIABETES

Bei jeder Untersuchung haben wir Dein Blut auf diabetesspezifische Autoantikörper untersucht. Diese Autoantikörper signalisieren einen beginnenden Angriff des Immunsystems auf den Pankreas (Bauchspeicheldrüse). Wir bestimmen vier Diabetes-Autoantikörper: IAA, GADA, IA-2A und ZnT8A (die ausführliche Bezeichnung aller Autoantikörper findest Du am Ende des Befundbriefes). Wie hoch Dein Risiko ist, einen Typ-1-Diabetes zu entwickeln, hängt davon ab, wie viele dieser Diabetes-Autoantikörper im Rahmen der TEDDY Studie bei Dir positiv getestet wurden. Deine aktuellen Autoantikörper Ergebnisse sind:

1a. Immer negativ:
Da Du innerhalb der letzten 15 Jahrekeine Diabetes-Autoantikörper entwickelt hast, ist es unwahrscheinlich, dass Du an Typ-1-Diabetes erkranken wirst. Die Wahrscheinlichkeit, Diabetes-Autoantikörper zu entwickeln, ist im Kleinkindalter (< 5 Jahre) am höchsten. Vereinzelt kann es vorkommen, dass sich Diabetes-Autoantikörper auch nach dem Alter von 15 Jahren entwickeln, aber das geschieht deutlich seltener. Wir empfehlen Dir, Dich mit den Symptomen für einen Typ-1-Diabetes vertraut zu machen und Deine Ärztin/Deinen Arzt aufzusuchen, falls Du Symptome bemerken solltest.

1b. Früher positiv:
Obwohl alle Deine Diabetes-Autoantikörper-Tests aktuell negativ sind, hattest Du auch positive Diabetes-Autoantikörper in der Vergangenheit. Dein Risiko für Typ-1-Diabetes kann etwas höher sein, als bei jemandem, der immer negativ war.Die Wahrscheinlichkeit Diabetes-Autoantikörper zu entwickeln, ist im Kleinkindalter (< 5 Jahre) am höchsten. Vereinzelt kann es vorkommen, dass sich Diabetes-Autoantikörper auch nach dem Alter von 15 Jahren entwickeln, aber das geschieht deutlich seltener. Wir empfehlen Dir, Dich mit den Symptomen für einen Typ-1-Diabetes vertraut zu machen und Deine Ärztin/Deinen Arzt aufzusuchen, falls Du Symptome an Dir bemerken solltest.

1c. Ein Diabetes-Autoantikörper positiv:
Ein einzelner Diabetes-Autoantikörper erhöht Dein Risiko an Typ-1-Diabetes zu erkranken. Innerhalb von 10 Jahren nach Auftreten des Autoantikörpers erkranken 15% der Kinder an Typ-1-Diabetes. Das erhöhte Risiko besteht auch nach den 10 Jahren. Die meisten Menschen mit nur einem positiven Diabetes-Autoantikörper entwickeln allerdings keinen Diabetes. Wir empfehlen Dir, Dich mit den Symptomen für einen Typ-1-Diabetes vertraut zu machen und diesen Befund Deiner Ärztin/Deinem Arzt vorzulegen.

1d. Mehrere Diabetes-Autoantikörper positiv:
Da zwei oder mehr Diabetes-Autoantikörper positiv sind, besteht ein frühes Stadium eines Typ-1-Diabetes. Die Zeit, bis erhöhte Blutzuckerwerte auftreten und eine Insulintherapie notwendig ist, variiert zwischen Monaten und Jahren. 70 % (70 aus 100) der Personen mit zwei oder mehreren Diabetes-Autoantikörpern entwickeln innerhalb

der nächsten 10 Jahre erhöhten Blutzucker und müssen mit einer Insulintherapie beginnen. Das erhöhte Risiko bleibt auch nach den 10 Jahren bestehen. Es ist sehr wichtig, dass Du die Symptome für einen Diabetes kennst und sofort Deine Ärztin/Deinen Arzt aufsuchst, falls Du Symptome an Dir bemerken solltest. **Auch hast Du die Möglichkeit, dass wir Dich weiterhin mit Kontrolluntersuchungen begleiten – damit wir Dir und Deiner Familie helfen, so gut wir können.**

Diese Befunde sagen nur etwas über Dein Risiko für Typ-1-Diabetes aus. Sie haben keine Aussagekraft über das Risiko für andere Diabetes Formen.

Es ist wichtig, dass Du mit den Typ-1-Diabetes Symptomen vertraut bist:

Typische Symptome für Typ-1-Diabetes:

- Vermehrter Durst
- Kraftlosigkeit, Müdigkeit
- Häufiges Wasserlassen
- Ungewöhnlicher Gewichtsverlust

Falls Du irgendwelche dieser Symptome an Dir selbst bemerkst, solltest Du sofort eine Ärztin oder einen Arzt aufsuchen. Durch eine frühe Diagnose lässt sich Typ-1-Diabetes optimal behandeln und es kann verhindert werden, dass es zu einer schweren Stoffwechselentgleisung (diabetische Ketoazidose = lebensbedrohliche Überzuckerung im Blut) kommt.

2. ZÖLIAKIE

Ab dem 2. Lebensjahr haben wir auch jährlich Dein Blut auf Zöliakie-Autoantikörper (tTG-Autoantikörper) untersucht.

Zöliakie ist eine Autoimmunerkrankung. Sie verursacht eine Entzündung im Dünndarm, wenn man Gluten zu sich nimmt. Gluten ist ein Protein, das in Weizen, Gerste und Roggen enthalten ist. Durch die Erkrankung werden Teile des Dünndarms zerstört. Dies führt dazu, dass die Nährstoffe nicht mehr richtig vom Körper aufgenommen werden können. Typische Symptome für eine Zöliakie sind chronische Verstopfung oder Durchfall. Diese Symptome können jedoch auch bei anderen Erkrankungen auftreten.

Deine aktuellen Zöliakie-Autoantikörper Ergebnisse sind:

2a. Immer negativ:
Deine tTG-Autoantikörper-Ergebnisse waren immer negativ. Zu diesem Zeitpunkt ist keine zusätzliche Nachbeobachtung nötig.

2b. Früher positiv
Obwohl Deine tTG-Autoantikörper-Werte momentan negativ sind, hattest Du schon positive Befunde in der Vergangenheit. Wir empfehlen, Deine Zöliakie-Autoantikörper gelegentlich bei Deiner Ärztin/Deinem Arzt kontrollieren zu lassen.

2c. Aktuell positiv:
Deine letzten Zöliakie-Autoantikörper-Befunde waren positiv. Ein positiver Befund bedeutet nicht zwingend, dass auch eine Zöliakie vorliegt, aber es besteht ein erhöhtes Risiko. Wir empfehlen daher, diese Ergebnisse mit Deiner Ärztin/Deinem Arzt zu besprechen. Eventuell ist es nötig, Deine Werte bei einer Fachärztin/einem Facharzt (Gastroenterologe) kontrollieren zu lassen.

2d. Diagnostizierte Zöliakie Im Rahmen der TEDDY-Studie wurde bei Dir eine Zöliakie diagnostiziert.
Bitte folge dafür weiterhin den Empfehlungen Deines behandelnden Arztes.

3. AUTOIMMUNE SCHILDDRÜSENERKRANKUNGEN

Seit 2016 testen wir im Rahmen der TEDDY-Studie auch Schilddrüsen-Autoantikörper einmal mit 8 Jahren und später mit 14 Jahren.

Deine aktuellen Schilddrüsen-Autoantikörper Ergebnisse (TPO-Autoantikörper) sind:

3a. Immer negativ:
Deine Ergebnisse für Schilddrüsen-Autoantikörper sind bisher immer negativ ausgefallen. Zu diesem Zeitpunkt ist also eine weitere Nachbeobachtung nicht nötig. Trotzdem solltest Du Deine Ärztin/Deinen Arzt aufsuchen, wenn Dir irgendwelche Symptome an Dir auffallen.

3b. Aktuell positiv:
Da Deine letzten Schilddrüsen- Autoantikörperergebnisse positiv ausgefallen sind, haben wir zusätzlich den TSH-Wert bestimmt. Dieser ist ein Hinweis dafür, wie gut Deine Schilddrüse arbeitet.

Mit normalem TSH-Spiegel:
Während Deine Schilddrüsen-Autoantikörper-Ergebnisse positiv ausgefallen sind, liegt Dein TSH Spiegel im Normbereich. Wir empfehlen daher, weiterhin den Empfehlungen Deiner Ärztin/Deines Arztes zu folgen und eventuell den TSH-Wert zu überprüfen. Außerdem solltest Du Dich mit den unten folgenden Symptomen für eine Schilddrüsenerkrankung vertraut machen. Kontaktiere Deine Ärztin/Deinen Arzt, falls Du Symptome an Dir bemerken solltest.

Frauen mit positiven Schilddrüsen-Autoantikörpern wird empfohlen, vor einer Schwangerschaft die Schilddrüsenwerte überprüfen zu lassen, da eine normale Schilddrüsenfunktion während der Schwangerschaft sehr wichtig ist.

3c. Aktuell positiv:
Da Deine letzten Schilddrüsen-Autoantikörper-Ergebnisse positiv ausgefallen sind, haben wir zusätzlich den TSH-Wert bestimmt. Dieser ist ein Hinweis dafür, wie gut Deine Schilddrüse arbeitet.

Mit auffälligem TSH-Spiegel:
Zusätzlich zu den positiven Schilddrüsen-Autoantikörpern ist auch der TSH-Wert nicht im Normbereich. Daher empfehlen wir, dass Dich Deine Ärztin/Dein Arzt für eine vollständige Untersuchung an eine Fachärztin/einen Facharzt (Endokrinologen) überweist.

Frauen mit positiven Schilddrüsen-Autoantikörpern wird empfohlen, vor einer Schwangerschaft die Schilddrüsenwerte überprüfen zu lassen, da eine normale Schilddrüsenfunktion während der Schwangerschaft sehr wichtig ist.

3d. Diagnostizierte autoimmune Schilddrüsenerkrankung (Schilddrüsenunterfunktion)
Während Deiner Teilnahme an der TEDDY-Studie wurde bei Dir eine autoimmune Schilddrüsenerkrankung (Schilddrüsenunterfunktion) diagnostiziert. Wir empfehlen, weiterhin Deine Werte von Deiner Ärztin/Deinem Arzt oder Endokrinologen kontrollieren zu lassen, um sicher zu gehen, dass Du die beste Versorgung bekommst.

Die Symptome für eine Hypothyreose (Schilddrüsenunterfunktion) können sehr unauffällig und auch mit anderen Erkrankungen verbunden sein. Die typischen Symptome sind:

- Vergrößerte Schilddrüse (Kropf)
- Müdigkeit
- Verminderte Leistung in der Schule
- Geringes Wachstum
- Trockene Haut
- Verstopfung
- Kälteunverträglichkeit
- Gestörter Menstruationszyklus
- Haarverlust

Symptome für eine Hyperthyreose (Schilddrüsenüberfunktion):

- Vergrößerte Schilddrüse (Kropf)
- Erhöhter Herzschlag
- Schlafprobleme
- Durchfall
- Gewichtsverlust
- Gesteigerter Appetit
- Vermehrtes Schwitzen
- Gestörter Menstruationszyklus

Durch Deine Teilnahme an der TEDDY-Studie können wir besser verstehen, welchen Einfluss das Immunsystem auf die Entwicklung von Typ-1-Diabetes und anderen Autoimmunerkrankungen hat. TEDDY ist die Grundlage für die Entwicklung von neuen Präventionstherapien, um die Entstehung von Typ-1-Diabetes, Zöliakie und Schilddrüsenautoimmunität zu verzögern oder sogar zu verhindern. Ohne Dich wäre das alles nicht möglich.
Vielen Dank!

Abkürzungen:
IAA = Insulin-Autoantikörper; GADA = Glutamat-Decarboxylase-Antikörper; IA-2A = Insel-Antigen-2 Autoantikörper; ZnT8A = Zink Transporter 8 Autoantikörper
tTGA= Tissue-Transglutaminase-Autoantikörper
TPO = Thyroidea Peroxidase-Autoantikörper
TSH = Thyreotropin

AAA. TEDDY Results Report programming requirements

Requirements for results categories in TEDDY Results Report (final version February 5, 2020)

1. Type 1 Diabetes Islet Autoantibodies	2. Celiac Disease tTG Autoantibody	3.Autoimmune Thyroid Disease TPO and TG Autoantibodies
a. Always Negative b. Previously Single Islet Autoantibody Positive, Most recently Negative c. Most recently Single Islet Autoantibody Positive d. Ever Multiple Islet Autoantibodies Positive	a. Always Negative b. Previously tTGA Positive, most recently Negative c. Most recently tTGA Positive d. Diagnosed with Celiac Disease while in TEDDY	a. Always Negative b. Most recently Autoantibody Positive with Normal TSH c. Most recently Autoantibody Positive with Abnormal TSH d. Diagnosed with Autoimmune Thyroid Disease while in TEDDY

For all results:

- The 14 year 6 month visit will be the last visit's results that will be used in the Results Report. This ensures that there is enough time to receive the results from the labs and generate the subject's Results Report so that it is ready for use by the 15 year visit.
- The Results Report will be able to be generated by the Clinical Centers three months from the close of the 14 year 6 month window. This ensures that all lab results have been uploaded to the DCC and that the report is ready in time for the first day of the 15 year visit window.
- The Results Report will only be able to be generated when the 14 year 6 month islet antibody results, 14 year transglutaminase antibody results and 14 year Thyroid antibody results are available or unusable sample status codes are indicated by the lab or not done reasons are entered in the tracking system by the Clinical Center for all three results.
- "Date of most recent testing" is the date of the last test ran for each of the three types of results (islet antibody, transglutaminase antibody, Thyroid antibody). The date will be the sample collection date of the last sample that was tested for that type.
- If a subject's results do not fit into one of the categories listed below in the Results Report "Unable to categorize results" will be listed under the corresponding section (Type 1 Diabetes Islet Autoantibodies; Celiac Disease tTG Autoantibody; Autoimmune Thryoid Disease TPO and TG Autoantibodies). The Clinical Centers will address these on a case by case basis.

1.Type 1 Diabetes Islet Autoantibodies, a. Always Negative:

- Check every visit from 3 months to 14 years 6 months

- Check that every single islet autoantibody result is negative (the subject has never had even one positive islet autoantibody)
    - NOTE: make sure that positive islet autoantibody results that have been deemed to be maternal autoantibodies are not considered positive for the child's results
- For MIAA, IA2A and GADA for US subjects only use the Denver lab results from the autoantibody reference lab sample
- For MIAA, IA2A and GADA for European subjects only use the Bristol lab results from the autoantibody reference lab sample

1.Type 1 Diabetes Islet Autoantibodies, b. Previously Single Islet Autoantibody Positive, Most recently Negative:

- Check every visit from 3 months to 14 years 6 months
- Check that the subject was deemed single persistent confirmed autoantibody positive which is defined as: islet autoantibody positive for only one autoantibody at two visits in a row, missed visits are okay, positivity does not need to be the same autoantibody to be classified as persistent (for example can be positive for GAD at 5 year visit and then positive for MIAA at 5 year 6 month visit and will be considered persistent positive) and same antibody is confirmed positive in other antibody lab
    - NOTE: if a subject was deemed multiple autoantibody persistent positive and even if subject has negative results afterward subject does NOT go in this category
    - NOTE: make sure that positive islet autoantibody results that have been deemed to be maternal autoantibodies are not considered positive for the child's results
- Check that the subject has been autoantibody negative for all islet autoantibodies for the last one year
- For MIAA, IA2A and GADA for US subjects only use the Denver lab results from the autoantibody reference lab sample
- For MIAA, IA2A and GADA for European subjects only use the Bristol lab results from the autoantibody reference lab sample
- For ZnT8A – the results are either from the autoantibody reference lab sample or the autoantibody repository sample (ZnT8A is measured in the Denver lab for both US and European subjects)

1.Type 1 Diabetes Islet Autoantibodies, c. Most recently Single Islet Autoantibody Positive:

- Check every visit from 3 months to 14 years 6 months
- Check that the subject was deemed single persistent confirmed autoantibody positive which is defined as: islet autoantibody positive for only one autoantibody at two visits in a row, missed visits are okay, positivity does not need to be the same autoantibody to be classified as persistent (for example can be positive for GAD at 5 year visit and then positive for

MIAA at 5 year 6 month visit and will be considered persistent positive) and same antibody is confirmed positive in other antibody lab
    - NOTE: make sure that positive islet autoantibody results that have been deemed to be maternal autoantibodies are not considered positive for the child's results
- Check that the subject has NOT been autoantibody negative for all islet autoantibodies for the last one year
- For MIAA, IA2A and GADA for US subjects only use the Denver lab results from the autoantibody reference lab sample
- For MIAA, IA2A and GADA for European subjects only use the Bristol lab results from the autoantibody reference lab sample
- For ZnT8A – the results are either from the autoantibody reference lab sample or the autoantibody repository sample (ZnT8A is measured in the Denver lab for both US and European subjects)

1.Type 1 Diabetes Islet Autoantibodies, d. Ever Multiple Islet Autoantibodies Positive:

- Check every visit from 3 months to 14 years 6 months
- Check that the subject was deemed multiple persistent confirmed autoantibody positive which is defined as: islet autoantibody positive for at least two autoantibodies at two visits in a row, missed visits are okay, positivity does not need to be the same autoantibody to be classified as persistent (for example can be positive for GAD and IA2A at 5 year visit and then positive for MIAA and IA2A at 5 year 6 month visit and will be considered persistent positive) and same antibodies are confirmed positive in other antibody lab
    - NOTE: make sure that positive islet autoantibody results that have been deemed to be maternal autoantibodies are not considered positive for the child's results
- No need to check for negative islet autoantibody results, as long as subject deemed multiple autoantibody persistent confirmed positive, subject will stay in this group
- For MIAA, IA2A and GADA for US subjects only use the Denver lab results from the autoantibody reference lab sample
- For MIAA, IA2A and GADA for European subjects only use the Bristol lab results from the autoantibody reference lab sample
- For ZnT8A – the results are either from the autoantibody reference lab sample or the autoantibody repository sample (ZnT8A is measured in the Denver lab for both US and European subjects)

2. Celiac Disease tTG Autoantibody, a. Always Negative:

- Check every visit from 2 years to 14 years 6 months (tTG autoantibodies are first tested at the 2 year visit)

- Check that subject was NEVER deemed tTGA persistent positive which is defined as: two consecutive TGA positive samples at any time (at the 24 month visit and on)
- For US subjects only use the Denver lab results from the autoantibody reference lab sample
- For European subjects only use the Bristol lab results from the autoantibody reference lab sample

2. Celiac Disease tTG Autoantibody, b. Previously tTGA Positive, most recently Negative

- Check every visit from 2 years to 14 years 6 months (tTG autoantibodies are first tested at the 2 year visit)
- Check that the subject was deemed tTGA persistent positive which is defined as: two consecutive TGA positive samples at any time (at the 24 month visit and on)
- Check that the last time that the subject was tested for tTGA the result was negative
- For US subjects only use the Denver lab results from the autoantibody reference lab sample
- For European subjects only use the Bristol lab results from the autoantibody reference lab sample

2. Celiac Disease tTG Autoantibody, c. Most recently tTGA Positive

- Check every visit from 2 years to 14 years 6 months (tTG autoantibodies are first tested at the 2 year visit)
- Check that the subject was deemed tTGA persistent positive which is defined as: two consecutive TGA positive samples at any time (at the 24 month visit and on)
- Check that the last time that the subject was tested for tTGA that the result was positive
- For US subjects only use the Denver lab results from the autoantibody reference lab sample
- For European subjects only use the Bristol lab results from the autoantibody reference lab sample

2. Celiac Disease tTG Autoantibody, d. Diagnosed with Celiac Disease

- Celiac disease diagnosis should be confirmed by review of the medical record. If the GI specialist or pediatrician makes a diagnosis of celiac disease, the clinical center should record this in the Chronic Illnesses section of the TEDDY Book as ICD-10 code K90.0. If the doctor suspects celiac disease and/or the parents suspect celiac disease, this is not the same as a diagnosis and should not be recorded in the Chronic Illnesses section.
- Check 3 month Interview, question #6.bb for ICD-10 code K90.0

- Check all TEDDY Book extraction forms submitted for the subject and look for ICD-10 code K90.0 in the Acute illnesses diagnosis section:
  - TEDDY book birth – 2 years, this is question # 8a
  - TEDDY book 2 – 5 years, this is question # 7a
  - TEDDY book 6 – 15 years, this is question # 6a
- Check all TEDDY Book extraction forms submitted for the subject and look for ICD-10 code K90.0 in the Chronic illnesses section:
  - TEDDY book birth – 2 years, this is question # 8b
  - TEDDY book 2 – 5 years, this is question # 7b
  - TEDDY book 6 – 15 years, this is question # 6b
- If a remission date is listed along with code K90.0 in the TEDDY Book chronic illness section, please also list the date of remission on the results report

<u>3.Autoimmune Thyroid Disease TPO and ThG Autoantibodies, a. Always Negative</u>

- Check results for Thyroid autoantibody samples collected at 8 years and 14 years
- Check that all (8 year and 14 year) TPO and ThG autoantibody results are negative (the subject has never had even one positive TPO or ThG autoantibody)
  - Do not check Thyroid autoantibody confirmatory results for this, some sites do not report these to the subjects
  - NOTE: Indeterminate TPOA and ThGA results: For results reporting to families, indeterminate results will be reported as negative results
- Both US and European subjects' thyroid samples are analyzed at the same lab – UF

<u>3.Autoimmune Thyroid Disease TPO and ThG Autoantibodies, b. Most recently Autoantibody Positive with Normal TSH</u>

- Check results for most recently collected Thyroid autoantibody sample – this could be either the 8 year sample (if the 14 year sample was not collected or low volume) or the 14 year sample
- Check that most recent sample (this could be either the 8 year sample (if the 14 year sample was not collected or low volume) or the 14 year sample) is positive for at least one thyroid autoantibody (TPO and/or ThG)
  - Do not check Thyroid autoantibody confirmatory results for this, some sites do not report these to the subjects
- Check that TSH result for most recent sample is normal (most recent sample is either the 8 year sample or 14 year sample – TSH is not run on the confirmatory sample)
- Both US and European subjects' thyroid samples are analyzed at the same lab – UF

<u>3.Autoimmune Thyroid Disease TPO and ThG Autoantibodies, c. Most recently Autoantibody Positive with Abnormal TSH</u>

- Check results for most recently collected Thyroid autoantibody sample – this could be either the 8 year sample (if the 14 year sample was not collected or low volume) or the 14 year sample
- Check that most recent sample (this could be either the 8 year sample (if the 14 year sample was not collected or low volume) or the 14 year sample) is positive for at least one thyroid autoantibody (TPO and/or ThG)
    - Do not check Thyroid autoantibody confirmatory results for this, some sites do not report these to the subjects
- Check that TSH result for most recent sample is abnormal (most recent sample is either the 8 year sample or 14 year sample – TSH is not run on the confirmatory sample)
- Both US and European subjects' thyroid samples are analyzed at the same lab – UF

3.Autoimmune Thyroid Disease TPO and ThG Autoantibodies, d. Diagnosed with Autoimmune Thyroid Disease

- Check 3 month Interview, question #6.bb for ICD-10 code E06.3
- Check all TEDDY Book extraction forms submitted for the subject and look for ICD-10 code E06.3 in the Acute illnesses diagnosis section:
    - TEDDY book birth – 2 years, this is question # 8a
    - TEDDY book 2 – 5 years, this is question # 7a
    - TEDDY book 6 – 15 years, this is question # 6a
- Check all TEDDY Book extraction forms submitted for the subject and look for ICD-10 code E06.3 in the Chronic illnesses section:
    - TEDDY book birth – 2 years, this is question # 8b
    - TEDDY book 2 – 5 years, this is question # 7b
    - TEDDY book 6 – 15 years, this is question # 6b
- If a remission date is listed along with code E06.3 in the TEDDY Book chronic illness section, please also list the date of remission on the results report

BBB.1. SITE SPECIFIC LETTER FOR REPORTING AUTOANTIBODY NEGATIVE RESULT AT 15 YEAR VISIT: COLORADO

Parent's Name
Address
Address
TEDDY ID

Dear Parents (or person who signed the informed consent),

We are writing to tell you about the autoantibody test results from (CHILD'S NAME)'s TEDDY study visit on (DATE OF LAST CLINIC VISIT) _____. This test is done every time we take a blood sample. The presence of autoantibodies is an early sign of an attack on the pancreas.

Your child's latest blood sample did not show any diabetes autoantibodies.

As you know, every child in TEDDY has the higher risk genes for type 1 diabetes. This means your child's lifetime risk is greater than children who do not have these genes.

This will be the last results you will receive from the TEDDY Study. If you have any questions about these test results or the TEDDY study, please call us at 303.724.7577.

Thank you for taking part in this important study.

Sincerely,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

BBB.2. SITE SPECIFIC LETTER FOR REPORTING AUTOANTIBODY NEGATIVE RESULTS AT 15 YEAR VISIT: GERMANY

HelmholtzZentrum münchen
Deutsches Forschungszentrum für Gesundheit und Umwelt

Klinikum rechts der Isar

Technische Universität München
Lehrstuhl für Diabetes und Gestationsdiabetes

Institut für Diabetesforschung · Heidemannastr. 1 · 80939 München

Univ.- Prof. Dr. med. Anette-Gabriele Ziegler
Direktorin
Institut für Diabetesforschung
Helmholtz Zentrum München

und

Forschergruppe Diabetes
Klinikum rechts der Isar
Technischen Universität München

Lehrstuhl für Diabetes und Gestationsdiabetes

und

Forschergruppe Diabetes e.V.
am Helmholtz Zentrum München

Annette Knopff
Telefon: 0800 - 3 38 33 39
Durchwahl: 089 / 3187 2546
Fax: 089 / 3187 3144
E-Mail:Annette.Knopff@helmholtz-muenchen.de
Teddy: www.teddy.epi.usf.edu

München, 13.03.2020

Sehr geehrte Familie xxx,

die Untersuchung der Diabetes-Autoantikörper vom xx.xx.xxxx bei xxx ergab folgendes Ergebnis:

Diabetes-Autoantikörper:

Name, Geburtsdatum

IAA:		Titer:		units (normal <0,95 units)
GADA:		Titer:		WHO units/ml (normal <33 WHO units)
IA2A:		Titer:		WHO units/ml (normal <5 WHO units)

Alle Diabetes-Autoantikörper liegen im Normbereich. Das bedeutet, dass gegenwärtig keine Inselautoimmunität und kein Typ 1 Diabetes vorliegt.

Die Wahrscheinlichkeit Diabetes-Autoantikörper zu entwickeln, ist im Kleinkindalter (< 5 Jahre) am höchsten. Vereinzelt kann es vorkommen, dass sich Diabetes-Autoantikörper auch nach dem Alter von 15 Jahren entwickeln, aber das geschieht deutlich seltener. Wir empfehlen Ihnen sich mit den Symptomen für einen Typ-1-Diabetes vertraut zu machen und eine Ärztin/einen Arzt aufzusuchen, falls Sie Symptome bemerken sollten.

Bei Fragen stehen wir Ihnen auch künftig gerne zur Verfügung.

Ihre Teilnahme an TEDDY war und ist eine sehr große Unterstützung bei der Erforschung der Ursachen von Typ-1-Diabetes. Vielen Dank!

Mit freundlichen Grüßen

Prof. Dr. med. Anette-G. Ziegler

Mehr zu unseren Studien unter:
www.aworldwithout1.de

Helmholtz Zentrum München
Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH)
Ingolstädter Landstr. 1
85764 Neuherberg
Telefon +49(0)89 3187 (0)
Telefax +49(0)89 3187 3322

info@helmholtz-muenchen.de
www.helmholtz-muenchen.de

Aufsichtsratsvorsitzende:
MinDir'in Prof. Dr. Veronika von Messling

Geschäftsführer:
Prof. Dr. med. Dr. h.c. Matthias H. Tschöp
Kerstin Günther

Registergericht:
Amtsgericht München HRB 6466
USt-IdNr- DE 129521671

Bankverbindung:
Münchner Bank eG
Konto-Nr. 2 158 620
BLZ 701 900 00
IBAN DE04701900000002158620
BIC GENODEF1M01

CCC. SITE SPECIFIC LETTER FOR REPORTING TRANSGLUTAMINASE AUTOANTIBODY NEGATIVE RESULT AT 15 YEAR VISIT: COLORADO

Parent's Name
Address
Address
TEDDY ID

Dear Parents (or person who signed the informed consent),

We are writing to tell you about the transglutaminase autoantibody test results from (CHILD'S NAME)'s TEDDY study visit on (DATE OF LAST CLINIC VISIT) _____. The transglutaminase antibody is used to screen people for celiac disease. Celiac disease is an autoimmune disease caused by a reaction to a protein found in wheat and wheat products.

We are writing to tell you that the result of the transglutaminase (TG) antibody test was **negative/positive**
Your results are:

This will be the last results you will receive from the TEDDY Study. If you have any questions about these test results or the TEDDY study, please call us at 303.724.7577.

Thank you for taking part in this important study.

Sincerely,

Marian J. Rewers, MD, PhD
Principal Investigator, TEDDY Study

DDD. SITE SPECIFIC LETTER FOR REPORTING RESULTS AT 15 YEAR VISIT IF SUBJECT CANNOT BE REACHED BY PHONE: SWEDEN

Till er som nu avslutat TEDDY studien

Vid ert sista besök blev ni lovade att få besked om de senaste provsvaren.

Eftersom vi inte kunnat nå er på telefon avslutas ert deltagande i TEDDY studien med detta brev.

☐ Analyserna visar att det finns inga autoantikroppar för autoimmun (typ 1) diabetes och celiaki.

☐ ----------

Om ni har frågor, vänligen kontakta er TEDDY sjuksköterska

Telefon:

Email:

17. Data Entry and Management

17.1. Data Management Section of TEDDY Website

17.1.1. Register Newborn

1) Complete clinical center specific screening form.
2) Go to TEDDY website: http://teddy.epi.usf.edu/
3) Click on "Register Newborn" under the Data Management heading on the left navigational bar.
4) Complete online screening form.
5) Required fields to save the form include (these fields are marked with a red"*"):
    - Child's date of birth
    - Local Code
    - Clinical Center
    - Visit Location Code - this is the location where the TEDDY visit took place. Drop-down list based upon TEDDY Clinical Center field.
    - Family History of T1DM
    - HLA Sample Draw Date
    - It is also required that the child's parents or legal guardians have signed the screening informed consent. This can be indicated on the online screening form.
6) Required fields to make the form complete (these fields are marked with a blue "*" and are in addition to the fields that are required to save the form):
    - Sex
    - Race
    - Ethnicity
    - Mother's date of birth
    - Study History
7) Once the form is complete click "Save", or "Save and Print" if you want a print out of the form.
8) A unique Subject ID will then be assigned to this individual and they will be registered in the study (the subject will have a status of "Registered"). This Subject ID number will appear at the top of the screening form next to the Local Code.

17.1.2. Enter/Edit/View

The Enter/Edit/View section leads you to a specific subject's 'Participant's Details Page':

1) Search for the desired subject by entering one of the following: 1) Local Code and Subject ID 2) Local Code and Date of Birth 3) Date of Birth Range 4) Clinical Center and Subject ID 5) Clinical Center and Local Code or 6) Clinical Center and/or Visit Location Code.

2) After a search method has been chosen you can also then Search by status of subject (Enrolled, HLA Eligible, HLA Not Eligible, etc.)
3) Under "Search Results" click on the Local Code of the desired subject (this will open the subject's 'Participant's Details Page').
4) From here you can access the subject's screening form, questionnaires, enrollment form, physical exam forms, and sample collection forms.

17.1.3. How to clear unwanted radio button choices

1) Position your mouse over the button that is incorrectly selected.
2) Click on the right side mouse button.
3) From the menu that appears, select 'Clear Answer'.
4) If the menu appears and you want to close it, select 'Close' to close the menu without clearing the answer.

17.1.4. Error messages displayed in online data entry forms and Sample Collection Forms

When entering data onto the online data entry forms and Sample Collection Forms you should make sure that no error messages appear when attempting to save the form. If you enter data, press 'Save' and an error message appears the data will not save until you correct all errors throughout the form. After you have corrected one error be sure to look and make sure that there are no additional error messages.

The error messages are in red and can be found:

1. in the data entry box at the top of the online data entry form where you enter 'date of interview', 'visit location code', etc (an example of an error that may appear here is Invalid Date)
2. in the actual questions of the online data entry form (for example an invalid age of the child may be highlighted in red with a pop-up window that says "Error invalid Range; Range is 1.5 – 26") and/or
3. at the very bottom of the form, you will have to scroll to the bottom of the form to see the error messages (an example of an error that may appear here is Error: Question 2r Other Codes: Row #1: Please enter a valid code and/or make sure codes are entered in uppercase letters.)
4. near the top of the Sample Collection Form

When you press 'save' unless a window pops up that says "Form successfully saved" and/or **Form submission successful.** is displayed at the bottom of the form you should look for error messages throughout the form.

17.1.5. Instructions for using Enrollment Form (activated 19/AUG/2005)

1) Login to the TEDDY Members website http://teddy.epi.usf.edu/

2) Click on 'Enter/Edit/View' under the section heading 'Data Management' on the left navigation menu.
3) Search for the desired subject by entering one of the following: 1) Local Code and Subject ID 2) Local Code and Date of Birth 3) Date of Birth Range 4) Clinical Center and Subject ID 5) Clinical Center and Local Code or 6) Clinical Center and/or Visit Location Code.
4) Under "Search Results" Click on the subject's Local Code to view that subject's Participant Details page. This page gives a list of all activities (forms, samples, etc.) done for a particular subject.
5) Scroll through this page until you find the Enrollment form, then click the 'View/Edit/Print' link under the title of that form.
6) Enter the Date of Contact, Visit Location Code (this is the location where the TEDDY visit took place. Drop-down list based upon TEDDY Clinical Center field) and TEDDY Staff Code.
7) Select one of the following radio buttons which pertains to informing the parent(s) of the child's increased risk of developing diabetes: 1) Date parent informed of child's increased risk (and then enter date) 2) Date letter sent to parents (and then enter date) 3) Parents never informed
8) Complete the form:
    a. To enroll a participant, click the 'Agreed to follow-up, informed consent signed'.
    b. To indicate a participant is not eligible based on exclusion criteria, select the 'Excluded' option and select the reason(s). If this form has been previously completed (before the 19 Aug 2005 version), and one of the "old answers" (an answer that does not map from the previous version of the form to the new version) is present (old answers will be in italics), it will appear as selected. You should uncheck the old answer(s) and attempt to select a new answer(s) that it corresponds to (if you are unsure about this, contact the DCC). Once all "old answers" are no longer selected, they will no longer appear on the form.
    c. To indicate a participant has refused enrollment, select the 'Refusal to enroll' option and select the reason(s). If this form has been previously completed (before the new version), and one of the "old answers" (an answer that does not map from the previous version of the form to the 19 Aug 2005 version) is present (old answers will be in italics), it will appear as selected. You should uncheck the old answer(s) and attempt to select a new answer(s) that it corresponds to (if you are unsure about this, contact the DCC). Once all "old answers" are no longer selected, they will no longer appear on the form.

9) Click 'Save' or 'Save & Print' to save the enrollment form, then 'Close' to close the form.
10) To edit this form, follow steps 1-5 above, then edit the form data as necessary (select a different enrollment option or add/delete reasons for a particular option) and click 'Save' or 'Save & Print', then 'Close' to close the form.

17.1.6. Sample Collection Forms

1) Logon to the TEDDY website http://teddy.epi.usf.edu/
2) Click on "Sample Collection Forms" link under "Data Management" on the left navigational toolbar.
3) Enter both the Subject ID and Local Code of the subject.
4) Select the desired visit.
5) Select the desired Sample Collection Form (i.e. serum, plasma, RNA, stool, etc).
6) See MOO section 14.1.7. for specific instructions on blood Sample Collection Forms; see MOO section 13.12. for specific instructions on water Sample Collection Forms; see MOO section 13.13. for specific instructions on toenail Sample Collection Forms; see MOO section 15.3. for specific instructions on stool Sample Collection Forms; see MOO section 13.14. for specific instructions on salivary cortisol Sample Collection Forms; see MOO section 13.15. for specific instructions on nasal swab Sample Collection Forms; see MOO section 13.6 for specific instructions on OGTT Sample Collection Forms; .

17.1.7. Data Upload

17.1.7.1 Submitting Scanned Forms

1) To submit scanned forms to the DCC, first login to the TEDDY Members website http://teddy.epi.usf.edu/
2) Click on 'Data Upload' under the 'Data Management' heading of the left navigation menu.
3) To upload the image files of your scanned forms, click the 'Browse…' button on the data upload page. This will give you a standard windows type explorer so you can find the files you wish to submit. Once you have found the file, click 'Open'.
4) Click 'Upload' to send the selected file to the DCC.
5) Once your submission is final you will see the name, upload status, and upload date/time of your file in the recent uploaded files list on this page

17.1.7.2. Submitting TEDDY Update Form Data for Incomplete Contact Attempts

File Naming Convention:

The files containing the TEDDY Update Form data should be named according to the following naming convention: **TUFCCCYYMMMDD.csv**

- The "TUF" is how the DCC will track which form the data applies to.
- The "CCC" is the three character code that identifies the Clinical Center (COL, FIN, GEO, GER, SWE or WAS).
- The "YYMMMDD" is the date the file is uploaded to the TEDDY website. ***NOTE: Year is first in the name in order for the DCC to sort the files by year. (Example: 14AUG31)**

File Type:

- All files should be uploaded as CSV files.

Order and Format of Data Fields in File:

Column headings of the CSV file should be in the following order and named as listed below:

- SubjectID
- LocalCode
- VisitLocationCode
- StaffID
- DateContactAttempt
- StatusContactAttempt

Data Field Definitions:

- SubjectID: Study identification number assigned to the subject by the DCC. The format of the Subject ID is a six digit number unique to the subject.
- LocalCode: Local identification number assigned to the subject by the Clinical Center. The format of the local code varies by site.
- VisitLocationCode: This is a three digit number assigned by the DCC associated with the location where the visit took place.
- StaffID: This is a four digit unique number assigned to the TEDDY staff member by the DCC.
- DateContactAttempt: Date of last contact attempt made. Date should be in DD/MMM/YYYY or DD-MMM-YYYY format.
- StatusContactAttempt: Site should enter one of the four digit numerical codes listed below to identify the status of the contact. Only the four digit numerical code should be indicated in the file, none of the descriptive language should be indicated in the file. If site needs to indicate more than one status code for the contact, please separate the

codes with a comma in between them as well as a space in between the comma and the code (for example: 9437, 9439).

9437 - Sent, not returned

9438 - Returned, not filled out

9439 - Contact attempted, no response

9440 - Unable to contact, no valid contact information

Uploading the file to the TEDDY website:

- Login to the TEDDY website
- Go to the "Data Upload" section which can be found under "Data Management" on the left navigational toolbar.
- In the "Filename" field you will see two buttons:
  - Click on the "Browse" button and locate the file you want to transmit to the DCC. Click on the desired file, and then click open. The file location and name should appear in the "Filename" field.
    (For example: C:/TEDDYStudy/Forms/ TUFCOL14AUG31.csv)
  - Once you have located the file you want to upload, click the "Upload" button.
- Once the file has been successfully uploaded the selected staff member(s) at the site will receive an automatic email from the DCC which contains the file name, date of upload, total number of records, number imported and number rejected.

17.1.8. Sample Shipment System

1) Logon to the TEDDY website, http://teddy.epi.usf.edu/
2) Go to the "Sample Shipment System" located on the left navigational toolbar under "Data Management".
3) Enter the date of shipment.
4) If you have user access to more than one shipment origin, you will need to choose which destination the samples you are shipping are being shipped from. If you only have user access to one shipment origin, the 'Origin' drop-down menu will be defaulted to that location and you do not need to do anything.
5) Choose the location where you are shipping samples to under "Destination": "HLA Reference Lab", "Autoantibody Lab", "Repository", "RNA Lab", "Cortisol Lab" or "HbA1c Lab" option under "Select where samples will be shipped to".
6) Enter the freezer box number for each box (numbers separated by commas) that you are going to be shipping that day and click "Search".

7) The Local Code, Subject ID, Clinical Center, Test Name, Vial Barcode Number, Visit Location Code, Date Draw, Box/Pouch Number, Space Number, Sample Volume, Site Number (this will only appear for samples being shipped to the Repository) and "Delete From Shipment" option will appear for all the samples that are located in the box(es).
8) Enter the tracking number and courier service for that shipment and any comments you would like to notify the lab about.
9) Click on "Print and Email Shipping List". A dialog box will open that asks "Are you sure you want to print and email the shipment list?" Press 'OK' if you do and 'Cancel' if you don't.
10) Once 'OK' has been clicked an Excel file will be created that will contain information pertaining to each sample (Vial Barcode Number, Subject ID, etc).
11) Save this file for your records; an email containing this file will automatically be sent to the DCC and to the location where the samples are being shipped.
12) Print out a copy of this list to be shipped with the samples.
13) Repeat this process as necessary until all the boxes you will be sending that day have been entered.

17.1.9. European Stool Sample System and Rectal Swab Sample System

TEDDY families enrolled in the study through the European sites (Germany, Finland, and Sweden) will send stool samples back to the clinical center (whereas US families will send stool samples directly to the Repository except for stool samples collected by rectal swab).

> NOTE: In August 2018 all stool sample collections were stopped on all subjects. Stool sample collection compliance was less than 20% in Europe and 15% in the US. The small numbers did not warrant the cost of collection, processing, nor the burden on the families.

<u>The European Clinical Centers and Clinical Centers collecting rectal swab samples will use the "European Stool Sample System and Rectal Swab Sample System" once they receive the stool samples back from the families:</u>

1) Logon to the TEDDY website http://teddy.epi.usf.edu/
2) Click on "European Stool Sample System and Rectal Swab Sample System" link under "Data Management" on the left navigational toolbar.
3) Place cursor in the "Vial Barcode Number" box.
4) Scan the preprinted barcode located on one of the stool tubes.
5) Enter the box number, space number, and date of collection for that tube.
6) Repeat steps 3-5 as necessary.

17.1.10. Search by Vial Barcode Number

This tool will mainly be used by the Repository when they receive stool samples from US families who forget to include the paperwork with the shipment (the paper work identifies the local code and subject ID associated with the sample). The purpose of this system is to allow the Repository to find out the local code, subject ID, visit location code, and clinical center associated with a particular sample by entering the vial barcode number of that sample.

17.2.Standard data collection forms

17.2.1. Downloading Blank Teleforms

1) Login to the TEDDY Members Website http://teddy.epi.usf.edu/
2) Click on "Data Forms" under "Study Forms" heading on the left navigation menu.
3) Open the questionnaire folder containing the teleform you wish to download.
4) Click on the teleform you would like to open (the teleforms are .PDF files)
5) To print this form right click on the open document and choose the print option. To save this form to your local computer/network, click 'Save As . . .' under "File".

17.2.2. Downloading and Printing prepopulated forms (single copy)

1) Login to the TEDDY Members Website http://teddy.epi.usf.edu/
2) Click on "Enter/Edit/View" under the section heading "Data Management" on the left navigation menu.
3) Search for the desired subject by entering one of the following: 1) Local Code and Subject ID 2) Local Code and Date of Birth 3) Date of Birth Range or 4) Clinical Center and/or Visit Location Code.
4) Under "Search Results", click on the Local Code of the desired subject to view that subject's Participant Details page. This page gives a list of all activities (forms, samples, etc.) done for a particular subject.
5) Scroll through this page until you find the form you wish to view or edit, then click the 'View/Edit/Print' link under the title of that form.
6) Click on the desired version of the teleform (English, Finnish, German or Swedish).
7) To print this form choose the print option under "File".

17.2.3. Downloading & Printing prepopulated forms (several at a time)

1) Login to the TEDDY Members Website http://teddy.epi.usf.edu/
2) Click on "Batch Print Forms" under the section heading "Data Management" on the left navigation menu.
3) Select the interval of time (based upon visit due date) by entering start and end dates.
4) Choose the subject (enter Local Code and Subject ID) OR

5) Choose set of subjects (enter Clinical Center only or both Clinical Center and Visit Location Code).
   NOTE: If a form has already been submitted for a subject, the form will not show up in the "Batch Print Forms" search results.
6) Choose the language you want the forms to print in from the language drop down list (or leave the default English for English forms). You must choose language **before** you click the "View Print List" button.
7) Click 'View Print List' button.
8) Check the forms you want to print or click the 'Select All Documents' box to select all forms.
9) Click 'Print Selected Documents' button to view the PDF file which you can then print or save to your local hard drive.

To print a batch of **TEDDY Update Forms** for your visit location:

1) Select both Clinical Center and Visit Location Code.
2) Choose the language you want the forms to print in from the language drop down list (or leave the default English for English forms). You must choose language **before** you click the "View Update Forms for VLC' button.
3) Click "View Update Forms for VLC" button.
4) Check the forms you want to print or click the "Select All Documents" box to select all forms.
5) Click "Print Selected Documents" button to view the PDF file which you can then print or save to your local hard drive.

17.2.4. Instructions for using the TEDDY Code Book

17.2.4.1. Finding the Code Book

1) Login to the TEDDY website http://teddy.epi.usf.edu/
2) Click on "TEDDY Code Book" under the "Study Management" section on the left navigational toolbar.
3) Search for the desired code and description or set of codes and descriptions by entering **one** of the following:
   a. TEDDY Code (e.g., CE001, MED00010)
   b. Description of the code (can enter code name, brand name, ingredient, producer, preparation, etc.)
   c. Form (choose the particular TEDDY questionnaire that you would like a list for of all codes that can be used on this form).
   d. Code group or category
4) Click 'Search' next to the criteria you entered. You can also click 'Show all codes' to see all codes or click 'Show recent codes' to see all codes added within the past two weeks.
5) A list of codes will appear under 'Search Result' with all of the details relevant to that code.

6) To download the results to an Excel spreadsheet, click 'Export to Excel'.

17.2.4.2. What to do when a code has not been assigned for a particular item

When a code has not been assigned for an item, email the DCC at teddy@epi.usf.edu. In the email provide the name of the item to be coded as well as the coding category (Reasons for Changing Baby's Formula, Types of Day Care, Types of Social Group, etc). The DCC will assign the item a code. If the item to be coded is questionable, the DCC will contact the appropriate person/committee to review the item.

If a proposed code item must be sent for review the clinical center staff member should use the 99999 (or 999.9 for ICD-10 codes or 99999999 for medication codes) code in the code box (codes that do not need to be reviewed will be assigned codes immediately). Once a decision has been made, and if a code is assigned, the clinical center staff member will have to go to the online version of the form and enter the new code.

17.2.4.3. Announcement of code book changes

Each clinical center will designate a person at their site to be the 'code book contact person'. When a change has been made to the TEDDY code book, this person will be notified and it is his/her responsibility to notify the appropriate people at his/her site about this change. If applicable, the DCC will also contact the person who initiated the coding process of this particular item. Newly coded items will also be listed by default on the 'TEDDY Code Book' search page on the TEDDY website.

17.2.5. Scanning Forms

1) Once you have a set of forms that have been completed you must scan them to create an electronic copy (image file) of the forms with the data on them.
2) Scan the forms using your local scanning setup. Save the image files of the scanned forms to a place you will later be able to retrieve them from so you can send to the DCC.
3) Make sure you name the file in accordance with the DCC's naming convention and that you save the file as a .TIF document. Teleform files should be named using the following format:

TFMyyyymondd_xx_ccc.tif

yyyy = year of date file is created (e.g. 2005)
mon = month of date file is created (e.g. MAR)
dd = day of date file is created (e.g. 24)
xx = file number that is being uploaded that particular day by the clinical center (e.g. if it is the first file the site has uploaded that

day this number would be 01, if it is the second it would be 02, etc.)
ccc = 3 letter code of the clinical center (e.g. SWE, GEO, etc.)

If a Clinical Center has more than one site that uploads teleform files to the TEDDY website, the site can include their visit location code in the name of the file by using the following format:

TFMyyyymondd_xx_vlc_ccc.tif

yyyy = year of date file is created (e.g. 2005)
mon = month of date file is created (e.g. MAR)
dd = day of date file is created (e.g. 24)
xx = file number that is being uploaded that particular day by the clinical center (e.g. if it is the first file the site has uploaded that day this number would be 01, if it is the second it would be 02, etc.)
vlc = 3 digit visit location code of the site (e.g. 401, 201, etc)
ccc = 3 letter code of the clinical center (e.g. SWE, GEO, etc.)

17.2.6. Submitting Form Data

1) To submit scanned forms to the DCC, first login to the TEDDY Members website.
2) Click on 'Data Upload' under the 'Data Management' heading of the left navigation menu.
3) To upload the image files of your scanned forms, click the 'Browse…' button on the data upload page. This will give you a standard windows type explorer so you can find the files you wish to submit. Once you have found the file, click 'Open'.
4) Click 'Upload' to send the selected file to the DCC.
5) Once your submission is final you will see the name, upload status, and upload date/time of your file in the recent uploaded files list on this page.

17.2.7. Viewing/Editing Online Data

1) Once your forms have been uploaded and processed, your data will be available for viewing and editing online (you will not be able to do this immediately after uploading the file; before the data can be seen online the DCC needs to process the files first).
2) To view or edit your form data, login to the TEDDY Members website.
3) Click on 'Enter/Edit/View' under the section heading 'Data Management' on the left navigation menu.
4) Search for a particular subject by entering that subject's Local Code, Subject Id, or search by Clinical Center.

5) Click on the subject's Local Code to view that subject's Participant Details page. This page gives a list of all activities (forms, samples, etc.) done for a particular subject.
6) Scroll through this page until you find the form you wish to view or edit, then click the 'View/Edit/Print' link under the title of that form.
7) You can now view, print, or change the form data. When complete, click 'Save' or 'Save & Print', then 'Close' to close the form.

17.2.8. Tracking System:

1) Logon to the TEDDY website http://teddy.epi.usf.edu
2) Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3) Search for the desired subject by entering one of the following: 1) Local Code and Subject ID 2) Local Code and Date of Birth 3) Date of Birth Range 4) Clinical Center and Subject ID 5) Clinical Center and Local Code or 6) Clinical Center and/or Visit Location Code.
4) Under "Search Results", click on the Local Code of the desired subject.
5) Choose the tracking page associated with the desired sample or form by clicking on the links under "Event Title" entitled "Tracking".
6) Once you have clicked on the tracking link a new page will open that is specific to the event that you clicked on.
7) Forms/Questionnaires:
    a. Submitted forms/questionnaires (excluding 3 Day Diet Records):
        i. When tracking system page is opened the following information, for that particular form/questionnaire, will be listed:
            - Event Status (complete or incomplete)
            - Event Date (For interviews this is the interview date, for self-administered questionnaires this is the date the questionnaire was filled out by the parent/primary caretaker, for the physical exam form this is the date of the exam, etc.)
    b. Submitted 3 Day Diet records:
        i. When tracking system page is opened the following information, for that particular Diet record, will be listed:

- Event Status (complete or incomplete)
- Event Date (this is date the diet record was completed)
- If the record is accepted and complete with a special circumstance the user will be able to choose the special circumstance from the drop down menu and then click "Save". Reasons include:
  - Mailed or faxed with telephone review
  - Includes illness day(s)
  - Mailed or faxed with telephone review and includes illness day(s)

c. Forms/Questionnaires (excluding 3 Day Diet Records – see d. for instructions) that have not been submitted:
   i. When tracking system page is opened if the form/questionnaire was completed, but the data has not been entered into the online system yet, the user will be able to enter the date that the form was completed (for 24 hour recalls this is the date the recall is completed with the parent– **NOTE**: US sites do not need to enter the date of completion in the tracking system for 24 hour recalls because the DCC can retrieve this date from NDS; European sites will need to enter the date of completion for 24 hour recalls in the tracking system, for interviews this is the interview date, for self-administered questionnaires this is the date the questionnaire was filled out by the parent/primary caretaker, for the physical exam form this is the date of the exam, etc.) **NOTE**: If you indicate a date of completion for the form/questionnaire, the task status for this event will show up as "Pending" on the Participant's Details Page.
   ii. If the form/questionnaire was not completed the user will be able to choose from the drop down menu the reason why the form/questionnaire has not been submitted. Reasons include:

- Unable to contact subject
- Parent refused
- Child refused
- Missed appointment
- Illness
- Subject was not 8 years old at time of visit (ONLY available in the 8 year pubertal assessment form tracking system)
- Child developmentally unable (ONLY available in the First and Annual Child and End of TEDDY Child Questionnaires' tracking system; this choice should be used by staff when child has a diagnosed condition such as mental retardation or autism that impacts their ability to complete the First/Annual/End of TEDDY Child Questionnaire. When parents state that they believe their child is "not mature enough" or "not ready" to complete the First/Annual/End of TEDDY Child Questionnaire at a particular visit, this should be indicated as "Parent refused")
- Other

NOTE: If you choose a reason for why the form/questionnaire was not completed, the task status for this event will show up as "Not Done" on the Participant's Details Page.

iii. User also has the ability to apply the date of completion or the not done reason to other items in the visit by clicking on the check box next to the desired item in the table at the bottom of the tracking system page. The information will be applied to the item associated with the tracking system page that is open as well as all items that are indicated by clicking on the corresponding check box.

iv. When date of completion has been entered or reason has been indicated and, if applicable, desired check boxes have been indicated click "Save Form".

d. 3 Day Diet Records that have not been submitted

i. When tracking system page is opened if the record was completed, but the data has not been sent to the DCC yet, the user will be able enter the date of completion for the 3 day diet record and then click "Save Form" – for the European sites "Date of Completion" means the date on which the 3 day diet record is reviewed with the parent. For the US sites "Date of Completion" means the date on which the 3 day diet record is reviewed with the parent and entered into NDS.
NOTE: US sites only need to enter the "Date of Completion" for 3 day diet records that are accepted with special circumstances; US sites do not need to enter the date of completion for 3 day diet records accepted without a special circumstance because the DCC can retrieve this date from NDS. European sites should enter the date of completion for all accepted 3 day diet records (for 3 day diet records accepted with or without special circumstances).

ii. If the record is not accepted because it was late, missing or incomplete the user will be able to choose from the drop down menu the reason why the record has not been submitted and then click "Save Form".
Reasons include:
- Family submitted too late
- Family submitted too early and did not correct
- Food or meals were incomplete
- Family missed appointment
- Parent refused
- Child refused
- Unable to contact family
- Other not specified

iii. If the record is accepted and complete with a special circumstance the user will be able to choose the special circumstance from the drop down menu and then click "Save Form".
Reasons include:
- Mailed or faxed with telephone review

- Includes illness day(s)
- Mailed or faxed with telephone review and includes illness day(s)

8) Samples:
   a. Submitted Sample Collection Forms (SCFs):
      i. When tracking system page is opened the following information, for that particular SCF, will be listed:
         - Event Date (date sample was drawn/collected)
         - Event Status (complete or incomplete)
      ii. For each aliquot the following information will be listed:
         - Test name
            - Results will be displayed in this section for Autoantibody Reference Lab Samples (for samples that the DCC has received results back from the local reference lab)
         - Vial barcode number
         - If applicable, insufficient volume will be indicated
         - If applicable, date sample shipped
         - If applicable, date received by DCC (date data was uploaded to the TEDDY website by the lab or repository)
         - If applicable, date sample processed (this only applies for blood samples sent to either the Autoantibody Reference Labs, RNA lab or HLA Reference Lab)
         - Whether or not the sample is usable (All samples are considered to be usable, unless otherwise indicated by repository or lab).
   b. SCFs that have not been submitted:
      i. When tracking system page is opened if the sample was collected, but the data has not been entered into the SCF yet, the user will be able enter the date that the sample was collected.

NOTE: If you indicate a date of completion for the sample, the task status for this event will show up as "Pending" on the Participant's Details Page.

ii. If the sample was not collected the user will be able to enter the reason why the sample was not collected. Reasons include:
    - Unable to contact subject
    - Parent refused
    - Child refused
    - Unable to obtain sample
    - Missed appointment
    - Illness
    - Stool sample was not collected within the assigned window
    - Urine sample not able to be processed within 24 hours due to long distance protocol collection
    - Other

    NOTE: If you choose a reason for why the sample was not collected, the task status for this event will show up as "Not Done" on the Participant's Details Page.

iii. User also has the ability to apply the date of completion or the not done reason to other items in the visit by clicking on the check box next to the desired item in the table at the bottom of the tracking system page. The information will be applied to the item associated with the tracking system page that is open as well as all items that are indicated by clicking on the corresponding check box.

iv. For stool samples, the user has the ability to apply the not done reason of "Parent refused" or "Child refused" to **all** stool samples for which no data has yet been submitted to the DCC. The reason this option has been added is because sites have indicated that some parents/subjects have refused to collect any or any more stool samples for TEDDY. Sites should only use this option if the parent/subject has specifically indicated that he/she will not collect any or any more stool samples for TEDDY:
    1. Open any stool sample tracking system for which no data has been submitted to the DCC.

2. Click on “Parent refused” or “Child refused” next to “Reason Not Completed”.
3. Check the box next to “Apply ‘parent/child refused’ reason to all the stool events”.

v. For urine samples, the user has the ability to apply the not done reason of “Parent refused” or “Child refused” or “Urine sample not able to be processed within 24 hours due to long distance protocol collection” to **all** urine samples for which no data has yet been submitted to the DCC. The reason this option has been added is because sites have indicated that some parents/subjects have refused to collect any or any more urine samples for TEDDY or the subject will always be a long distance protocol subject and the site is not able to process the sample in time. Sites should only use this option if the parent/subject has specifically indicated that he/she will not collect any or any more urine samples for TEDDY or if it is known the site cannot process the sample in time:
    1. Open any urine sample tracking system for which no data has been submitted to the DCC.
    2. Click on “Parent refused” or “Child refused” or “Urine sample not able to be processed within 24 hours due to long distance protocol collection” next to “Reason Not Completed”.
    3. Check the box next to “Apply ‘parent/child refused’ reason to all the urine events” or “Apply 'urine sample not able to be processed within 24 hours due to long distance protocol collection' reason to all the urine events”.
vi. When date of completion has been entered or reason has been indicated and, if applicable, desired check boxes have been indicated click “Save Form”.

17.2.9. Entering data when date of completion/collection is outside of visit window

Occasionally Clinical Centers will need to enter forms, questionnaires and/or Sample Collection Forms that were collected outside of a subject's visit window. Reasons for this may include: Post-diagnosis visit after subject is diagnosed with T1D; subject becomes autoantibody positive and changes from 6 month visit schedule to 3 month visit schedule; due to limited availability of subject's schedule subject completed two TEDDY visits within the same window, etc.

For these situations, at the time of data entry, if the window for a sample collected or a form/questionnaire completed is not in the future, but the actual date of collection or date of form completion is still outside of the allotted window, the Clinical Center should enter the data on the corresponding form and enter a date of collection/interview date/review date that falls within the window so that the form can be saved. Once the Clinical Center has entered the information they should contact the DCC with the correct date of collection/interview date/review date so that the DCC can update the date in its database. The Clinical Center should email the following information to the DCC when making this request:

- Subject ID
- Local Code
- Sample name(s), visit(s) and correct date(s) of collection for sample(s) collected at visit
- Form name(s), visit(s) and correct interview date(s)/review date(s) for form(s)/questionnaire(s) completed at visit

If a window has not yet opened (the window consists of future dates) for a sample collected or a form/questionnaire completed, the Clinical Center should contact the DCC to open the window so that the data can be entered. The Clinical Center should email the following information to the DCC when making this request:

- Subject ID
- Local Code
- Sample name(s), visit(s) and correct date(s) of collection for sample(s) collected at visit
- Form name(s), visit(s) and correct interview date(s)/review date(s) for form(s)/questionnaire(s) completed at visit

The DCC will notify the site when the window has been changed and they are able to enter the data. The site should immediately enter the data and let the DCC know when the data entry has been completed so that the window can be immediately changed back.

Sites should mark all errors related to dates associated with these date/window changes in the Error Reporting and Verification System (ERVS) as verified.

17.2.10. Instructions for using the Withdrawal of Screening Consent Form

1) The Withdrawal of Screening Consent form is only to be used for those participants who withdraw consent for the screening portion of the study, not the follow up. For those refusing consent of the follow up portion of the study, please complete the Enrollment Form.
2) Login to the TEDDY Members website.
3) Click on 'Enter/Edit/View' under the section heading 'Data Management' on the left navigation menu.
4) Search for the desired subject by entering one of the following: 1) Local Code and Subject ID 2) Local Code and Date of Birth 3) Date of Birth Range 4) Clinical Center and Subject ID 5) Clinical Center and Local Code or 6) Clinical Center and/or Visit Location Code.
5) Under 'Search Results' Click on the subject's Local Code to view that subject's Participant Details page. This page gives a list of all activities (forms, samples, etc.) done for a particular subject.
6) Select 'Withdrawal of Screening Consent' from the drop down list under 'Additional Study Forms' heading and click 'Select Form'.
7) Enter the TEDDY Staff Code, Date of Withdrawal, and explanation of why the participant has chosen to withdraw consent.
8) Click 'Save' or 'Save & Print' to save the Withdrawal of Screening Consent form, then 'Close' to close the form.
9) Once you have saved the form, the DCC will review the request to have the subject withdrawn. Once the DCC has either approved or denied the withdrawal request, you will receive an email notification. If the request is approved, the status of the participant will change to 'Withdrawn Screening Consent'.

17.2.11. Instructions for using the Change in Study Participation Form

1) Logon to the TEDDY website http://teddy.epi.usf.edu/
2) Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3) Search for the desired subject.
4) Under "Search Results", click on the Local Code of the desired subject.
5) Choose "Change in Study Participation Form" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
6) Click 'Select Form' button that is below dropdown menu.
7) Enter information, click the Save button and close the form.

Once the Participant's Details Page has been refreshed, you will see "Change in Study Participation Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1) Click on the form link under 'Completed Additional Study Forms'
2) A new window will open which will have links to all of the "Change in Study Participation Forms" that have been saved for this subject.
3) Click on an 'event date' link to open up a specific form for this subject.

17.2.12. Instructions for using the Parent Experiences Questionnaire/Child Experiences Questionnaire

1) Logon to the TEDDY website http://teddy.epi.usf.edu/
2) Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3) Search for the desired subject.
4) Under "Search Results", click on the Local Code of the desired subject.
5) Choose " Parent Experiences Questionnaire" or "Child Experiences Questionnaire" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
6) Click 'Select Form' button that is below dropdown menu.
7) You can print the Teleform from here and/or enter information, click the Save button and close the form.

You will notice on the online Parent Experiences Questionnaire and Child Experiences Questionnaire that there is a "Form Status" section at the top of the form. This section consists of four radio buttons:

- Sent out (when a Parent Experiences Questionnaire is sent to both the mother and the father, only one entry of "sent out" needs to be indicated)
- Returned but not filled out
- Unable to contact (no correct address, unable to deliver mail)
- Not sent out

"Returned but not filled out" is to be used by the DCC (for US subjects) and by the designated neutral locations (for European subjects), if necessary. The other three choices are to be used by the clinical centers, if necessary.

Once a Parent Experiences Questionnaire/Child Experiences Questionnaire has been submitted (by either the DCC for US

subjects, or the neutral location for European subjects) clinical centers will see " Parent Experiences Questionnaire" and/or "Child Experiences Questionnaire" under 'Completed Additional Study Forms' near the top of the Participant's Details Page. However only the DCC will be able to open and view the submitted form. Multiple forms can be submitted for each subject.

17.2.13. Instructions for using the Diagnosis of Type 1 Diabetes Form

Once the TEDDY subject has been diagnosed with Type 1 Diabetes the Diagnosis of Diabetes Form should be completed.

Note: it is not necessary to complete a Change in Study Participation Form when a Diagnosis of Type 1 Diabetes Form has been submitted for the subject.

Note: if a child develops type 1 diabetes after they have withdrawn from the study a Diagnosis of Type 1 Diabetes Form should be completed.

Note**:** If the subject is diagnosed with Type 1 Diabetes after the close of the 15 year visit window, a Diagnosis of Type 1 Diabetes form should **NOT** be completed as the subject has finished the study and we are no longer collecting data from the subject.

1) Logon to the TEDDY website http://teddy.epi.usf.edu/
2) Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3) Search for the desired subject
4) Under "Search Results", click on the Local Code of the desired subject.
5) Choose "Diagnosis of Type 1 Diabetes" form that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
6) Click 'Select Form' button that is below dropdown menu.
7) You can print the Teleform from here and/or enter information (see MOO section 13.7 for detailed instructions on entering data on the Diagnosis of Type 1 Diabetes Form), click the Save button and close the form.
8) Once the form has been saved the subject's sub-status will change to "Enrolled (Diabetic)".

Once the Participant's Details Page has been refreshed, you will see "Diagnosis of Type 1 Diabetes" form under 'Completed Additional Study Forms' near top of Participant's Details Page:

1) Click on the form link under 'Completed Additional Study Forms'

2) A new window will open which will have a link to the "Diagnosis of Type 1 Diabetes Form" that has been saved for this subject.
3) Click on the 'View/Edit/Print" link to open up the specific form for this subject.

17.2.14. Instructions for using the Diagnosis of Non-Type 1 Diabetes Form

The "Diagnosis of Non-Type 1 Diabetes" form should be completed when a subject is diagnosed with some other type of diabetes other than Type 1, such as Type 2, MODY, CFRD, etc. The form should be completed with all information that is attainable by the TEDDY Staff. All fields with a red * are required to successfully save the form.

How to get to the Diagnosis of Non-Type 1 Diabetes Form

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject.
4. Under "Search Results", click on the Local Code of the desired subject.
5. Choose "Diagnosis of Non-Type 1 Diabetes" form that is in the "Additional Study Forms" dropdown menu at the upper right-hand corner of the Participant's Details Page.
6. Click 'Select Form' button that is below dropdown menu.
7. Enter information, click the Save button and close the form.

Once the Participant's Details Page has been refreshed, you will see "Diagnosis of non-Type 1 Diabetes" form under 'Completed Additional Study Forms' near top of Participant's Details Page:

1. Click on the form link under 'Completed Additional Study Forms'
2. A new window will open which will have a link to the "Diagnosis of Non-Type 1 Diabetes Form" that has been saved for this subject.
3. Click on the 'View/Edit/Print" link to open up the specific form for this subject.

17.2.15. Instructions for using the Participant in Non-TEDDY Research Form

If a TEDDY subject is currently participating or has participated in another research study, besides TEDDY, the site should use the Participant in Non-TEDDY Research Form to collect information about the study. The form should be completed by the TEDDY staff member. **If study participation is ongoing, the form should be filled out at each subsequent visit until the subject's participation has ended**. A radio button has been provided for "No change since last submittal of form" for questions 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14 to be used for situations when a Participant in Non-TEDDY Research Form has

already been submitted to the DCC and the study information has not changed since the last submittal of the form; date form completed, visit location code, TEDDY staff code and question #1 must always be completed. When a subject indicates that participation in the other study has ended, no further documentation is required. Obtain the answers for questions 1-5 from the parent or primary caretaker; obtain the answers for questions 6-14 from a staff member from the other study that the TEDDY subject is enrolled in.

Note: For question #6 ("Number of study visits per year") enter the average number of visits per year. If the average is 1 visit every 2 years, enter 0.5 visits per year (do not round up to the whole number).

Note: Please see information below regarding question numbers 10 (medications), 12 (vaccines) and 14 (dietary supplements) of the Non-TEDDY Research Form:

Some TEDDY children participate in research studies other than TEDDY. Some of these other studies have included blinded dietary supplements, blinded medications or blinded vaccines that become unblinded and revealed at the end of the study. TEDDY codes have been created to capture the blinded supplement, medication or vaccine when reported. Examples include:

B5162	Baby/Child Dietary Supplements (Sweden) (B)	a3 - Probiotic				Swedish: Blinded Research Probiotic	21 Nov 2011	Active
MED00675	Medications (MED)					English: Blinded Homeopathic Preparation	24 Sep 2007	Active
MED00799	Medications (MED)					English: Blinded Research Medication	16 Apr 2008	Active
V0032	Vaccines (V)					English: Blinded Research Vaccine	17 Jul 2007	Active

3 AUG 2012 Clinical Implementation Committee coding decision for blinded vaccines:

A Finnish vaccination research has ended and the participants have been informed which vaccination the child received. The vaccination was previously saved to the TEDDY Book with code V0032: Blinded Research Vaccine. Now that it is known which vaccine the child actually received, do we need to change the codes in the TEDDY Book? How do we handle the Participant in Non-TEDDY Research Form?

The "Blinded Research Vaccine" code will continue to be stored in the database for these subjects. No changes need to be made to this code entered on the forms. However, the committee does want to know the components of the vaccine given in the study and wants it indicated in the code that that particular vaccine was given as part of the vaccination

research study. Therefore, new vaccine codes will be created for these and the following statement will be indicated in the code details along with the component(s) of the vaccine: "(Administered as part of vaccination research study)".

Examples include:

V0058	Vaccines (V)						English: Hepatitis A vaccine (Administered as part of vaccination research study) Finnish: Hepatiitti A -rokotus (Rokotettu osana rokotetutkimusta) BrandNameFin: Havrix	14 Aug 2012	Active
V0059	Vaccines (V)						English: Hepatitis B vaccine (Administered as part of vaccination research study) Finnish: Hepatiitti B -rokotus (Rokotettu osana rokotetutkimusta) BrandNameFin: Engerix B	14 Aug 2012	Active

In order to be consistent with the coding decision above that was made for the blinded vaccines, in January 2019 fields were added to the Non-TEDDY Research Form in order to capture all data for unblinded medications, vaccines and dietary supplements on the Non-TEDDY Research Form:

- Question #10 Medications:
  - Medication code (use either TEDDY Code that lists active ingredients of unblinded medication with indication in code details of "*Administered as part of medication research study*" or TEDDY Code "MED01370: Placebo Medication (Administered as part of medication research study)")
  - Reason for medication (always use ICD-10 code "Z00.6: Clinical Research Investigation")
  - How old was your child when they received this medication?
  - For how many days did you give the medication?
  - Was the medication information parent reported or research study confirmed?
- Question #12 Vaccines:
  - Vaccine code (use either TEDDY Code that lists the components of unblinded vaccine with indication in code details of "*Administered as part of vaccination research study*" or TEDDY Code "V0070: Placebo Vaccine (Administered as part of vaccination research study)")
  - Date of vaccine
  - Was the vaccine information parent reported or research study confirmed?
- Question #14 Dietary Supplements:
  - Dietary Supplement code (use either TEDDY Code that lists the components of unblinded dietary supplement with indication in code details of "*Administered as part of dietary supplement research study*" or TEDDY Swedish Code

"B5399: Placebo Dietary Supplement (Administered as part of dietary supplement research study)" or TEDDY Finnish Code "35912: Placebo Dietary Supplement (Administered as part of dietary supplement research study)" or TEDDY German Code "B3205: Placebo Dietary Supplement (Administered as part of dietary supplement research study)" or TEDDY US Code "B888: Placebo Dietary Supplement (Administered as part of dietary supplement research study)"*)*

- Drops, mL, tablets, other
- How many times a week?
- Started
- Stopped
- Was the dietary supplement information parent reported or research study confirmed?

Listed below are the details for recording the data for all types of medications, vaccines and dietary supplements given through a research study:

- Blinded medications, vaccines and dietary supplement data should be recorded in both the TEDDY Book and the Non-TEDDY Research Form
  - Remember to record the end date information for the medications and dietary supplements in both forms as well
- Unblinded medications, vaccines and dietary supplement data only needs to be recorded in the Non-TEDDY Research Form from January 2019 and on
  - For unblinded medication, vaccine and dietary supplement data entered in the TEDDY Book prior to January 2019 – no changes have to be made to previously entered data, the DCC will pull the data from both forms.
- Medications, vaccines and dietary supplements that were never blinded to the subject should be recorded in both the TEDDY Book and the Non-TEDDY Research Form
  - Remember to record the end date information for the medications and dietary supplements in both forms as well

1) Logon to the TEDDY website http://teddy.epi.usf.edu/
2) Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3) Search for the desired subject
4) Under "Search Results", click on the Local Code of the desired subject.
5) Choose "Non-TEDDY Research Form" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
6) Click 'Select Form' button that is below dropdown menu.

7) You can print the Teleform from here and/or enter information, click the Save button and close the form.
8) Once the Participant's Details Page has been refreshed, you will see "Non-TEDDY Research Form" form under 'Completed Additional Study Forms' near top of Participant's Details Page:
9) Click on the form link under 'Completed Additional Study Forms'
10) A new window will open which will have a link to the "Non-TEDDY Research Form" that has been saved for this subject.
11) Click on the 'View/Edit/Print" link to open up the specific form for this subject.

17.2.16. Instructions for using the OGTT Sample Collection Form

For children between the ages of 1 year and 3 years who have elevated random or fasting glucose levels, sites have the option of performing an OGTT on the child. An OGTT performed on a child less than 3 years of age is completely optional and left to the discretion of the site. For only these subjects the site should follow the SCF instructions below.

For subjects who meet the following requirements the OGTT SCF will display in the Participant's Details Page schedule (as described in section 17.1.6.): An OGTT test will be performed every six months on every child who has tested positive for two or more autoantibodies, regardless of autoantibody positivity confirmation or persistence, at any previous visit (but both antibodies must be positive at the same visit) and is three years of age or older.

1) Logon to the TEDDY website http://teddy.epi.usf.edu/
2) Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3) Search for the desired subject
4) Under "Search Results", click on the Local Code of the desired subject.
5) Choose "OGTT Sample Collection Form" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
6) Click 'Select Form' button that is below dropdown menu.
7) Enter information (see MOO section 13.6 for detailed instructions on OGTTs and entering data on the OGTT Sample Collection Form), click the Save button and close the form.

Once the Participant's Details Page has been refreshed, you will see "OGTT Sample Collection Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1) Click on the form link under 'Completed Additional Study Forms'

2) A new window will open which will have a link to the "OGTT Sample Collection Form(s)" that has been saved for this subject.
3) Click on the 'View/Edit/Print" link to open up the specific form for this subject.

17.2.17. Instructions for using the Positive Transglutaminase Antibody Follow-Up/Biopsy Form

The TEDDY "Positive Transglutaminase Antibody Follow-Up/Biopsy Form" should be completed for all children who have persistent positive TGA (at the 24 month visit and on) or who were diagnosed with Celiac disease outside of the TEDDY study. Persistence is defined as having two consecutive TGA positive samples at any time (at the 24 month visit and on). If biopsy did occur, then indicate outcome on the form, if no biopsy occurred then document reasons why not. More than one form should be submitted per subject if biopsies have been performed on several occasions or the biopsy data has changed. The DCC will create a report which lists the subjects who have persistent positive TGA (at the 24 month visit and on) to help the Clinical Centers determine which subjects need this form completed. As the DCC does not know which subjects were diagnosed with Celiac disease outside of the TEDDY study until this form is completed, these subjects will of course not be listed on the report and it is the site's responsibility to remember to complete this form for these subjects. The site will know about the Celiac disease diagnosis when the parent indicates Celiac disease in the Chronic Illness section of the TEDDY Book- please note that site should indicate ICD-10 code K90.0 (see section 17.2.15.1) - and at that time the site should complete the "Positive Transglutaminase Antibody Follow-Up/Biopsy Form".

1) Logon to the TEDDY website http://teddy.epi.usf.edu/
2) Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3) Search for the desired subject
4) Under "Search Results", click on the Local Code of the desired subject.
5) Choose "Positive Transglutaminase Antibody Follow-Up/Biopsy Form" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
6) Click 'Select Form' button that is below dropdown menu.
7) You can print the Teleform from here and/or enter information, click the Save button and close the form.

Once the Participant's Details Page has been refreshed, you will see "Positive Transglutaminase Antibody Follow-Up/Biopsy Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1) Click on the form link under 'Completed Additional Study Forms'
2) A new window will open which will have a link to the "Positive Transglutaminase Antibody Follow-Up/Biopsy Form" that has been saved for this subject.
3) Click on the 'View/Edit/Print" link to open up the specific form for this subject.

Tracking System instructions for "Positive Transglutaminase Antibody Follow-Up/Biopsy Form"

If the site is unable to collect data for the form, the site should mark a not done reason in the tracking system of the form:

1) Go to the corresponding form:
    a) Choose "Positive Transglutaminase Antibody Follow-Up/Biopsy Form" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
    b) Click 'Select Form' button that is below dropdown menu.
2) Select "Tracking System" button at top of form.
3) A new window will open which allows the site to enter the reason why the form was not completed.
4) Once the not done reason has been selected, click "Save Form".

Once the Participant's Details Page has been refreshed, you will see "Positive Transglutaminase Antibody Follow-Up/Biopsy Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1) Click on the form link under 'Completed Additional Study Forms'
2) A new window will open which will have a link to the tracking system form that has been saved for this subject.
3) Click on the 'Tracking' link to open up the specific tracking system form for this subject.

17.2.15.1. Celiac Disease Diagnosis

Celiac disease diagnosis should be confirmed by review of the medical record. If the GI specialist or pediatrician makes a diagnosis of celiac disease it should be recorded in the Chronic Illnesses section of the TEDDY Book as ICD-10 code K90.0. If the doctor suspects celiac disease and/or the parents suspect celiac disease, this is not the same as a diagnosis and should not be recorded in the Chronic Illnesses section. If the subject is on a gluten free diet due to suspected celiac disease, this should be captured in the Special Diets Section of the TEDDY Book and coded as SDM09 or SDM16 as appropriate. The special diet indication

does not mean that a "Tracking Form: Gluten-free Diet Annual Update Form" or the "Positive Transglutaminase Autoantibody Follow-Up/Biopsy Form" should be completed. However, these forms should be completed if the subject meets the requirements listed in section 16.2.2.

17.2.18. Instructions for using the TEDDY Update Form

The TEDDY Update Form should be completed annually for TEDDY participants who have either:
1) Actively withdrawn from the study and have agreed to future contact
2) Became inactive participants by not responding to contact attempts (did not request to withdraw and were not asked about future contact)

For further details see MOO section 8.

1) Logon to the TEDDY website http://teddy.epi.usf.edu/
2) Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3) Search for the desired subject
4) Under "Search Results", click on the Local Code of the desired subject.
5) Choose "TEDDY Update Form" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
6) Click 'Select Form' button that is below dropdown menu.
7) You can print the Teleform from here and/or enter information, click the Save button and close the form.

Once the Participant's Details Page has been refreshed, you will see "TEDDY Update Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1) Click on the form link under 'Completed Additional Study Forms'
2) A new window will open which will have a link to the "TEDDY Update Form" that has been saved for this subject.
3) Click on the 'View/Edit/Print" link to open up the specific form for this subject.

17.2.19. Instructions for using the Long-Distance Protocol Registration Form

The Long-Distance Protocol Registration Form should be completed for all subjects who are on the Long-Distance Protocol. The site should indicate the date the subject was placed on the Long-Distance protocol in the corresponding field on the form. Once the form has been saved with this date the status of the subject will change to "Enrolled (Long-Distance Protocol)" and the DCC will then apply

"Long Distance Protocol collection" to all TEDDY forms and diet records collected for the subject on or after this date. Please note that site should still continue to complete the Long-Distance protocol sections on the Physical Exam Form and Sample Collection Forms.

If the subject is removed from the Long-Distance Protocol because he/she has moved back to an area with a participating TEDDY clinic or he/she is able to be in an area with a participating TEDDY clinic at times of scheduled visits, the site should enter the date the subject was removed from the Long-Distance Protocol in the corresponding field on the form (this date can be indicated on the same form that the "date subject placed on Long-Distance protocol" was entered on). Once the form has been saved with this date the status of the subject will change back to "Enrolled" and the DCC will then no longer apply "Long-Distance Protocol collection" to any forms and diet records collected for the subject on or after this date.

If after being removed from the Long-Distance Protocol, the subject moves again and needs to be placed back on the Long-Distance Protocol, the site should complete a NEW "Long-Distance Protocol Registration Form".

If the subject attended an in-person visit at a TEDDY clinic after he/she was placed on the Long-Distance protocol, mark each form and/or diet record in the corresponding field(s) that was not completed through the Long-Distance protocol (after he/she was placed on the Long-Distance protocol; these indications can be marked on the same form that the "date subject placed on Long-Distance protocol" was indicated on). Please note that this is only for subjects who remain on the Long-Distance Protocol, but who occasionally attend an in-person visit at a TEDDY clinic. Note that neither the physical exam form nor any of the sample collection forms are listed because each of these forms have long-distance protocol tracking fields on them.

1) Logon to the TEDDY website http://teddy.epi.usf.edu/
2) Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3) Search for the desired subject
4) Under "Search Results", click on the Local Code of the desired subject.
5) Choose "Long-Distance Protocol Registration Form" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
6) Click 'Select Form' button that is below dropdown menu.
7) You can enter the information, click the Save button and close the form.

Once the Participant's Details Page has been refreshed, you will see "Long-Distance Protocol Registration Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1) Click on the form link under 'Completed Additional Study Forms'
2) A new window will open which will have a link to the "Long-Distance Protocol Registration Form" that has been saved for this subject.
3) Click on the 'View/Edit/Print" link to open up the specific form for this subject.

17.2.20. Instructions for using the Biological Mother, Father and Sibling DNA Sample Collection Forms

1) Logon to the TEDDY website http://teddy.epi.usf.edu/
2) Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3) Search for the desired subject
4) Under "Search Results", click on the Local Code of the desired subject.
5) Go to the corresponding Sample Collection Form:
   i. These SCFs can be found under the Additional Study Forms drop-down menu at the upper right-hand corner of the Participant's Details Page – you will find a separate form for each relative: "Biological Father's DNA Sample Collection Form", "Biological Mother's DNA Sample Collection Form" and "Sibling's DNA Sample Collection Form" (if the TEDDY subject has multiple siblings that samples have been collected from, choose a new sibling SCF for each sibling).
   ii. Choose the desired form and click the "Select Form" button that is below the dropdown menu.
   iii. If the family only has one child enrolled in the TEDDY study:
      1. Enter the sample information on the corresponding family member's SCF and answer the questions at the bottom of the form. Leave the family ID field blank – it will be automatically assigned by the DCC at the time of the first save of any of the family member SCFs. Also leave the Relative ID field blank, an ID specific to that family member will also be assigned by the DCC at the time of the save of the SCF.
      2. Click the save button and close the form.
      3. Repeat this as necessary for each family member that samples have been collected from.
   iv. If the family has more than one child enrolled in the TEDDY study, samples only need to be collected from each family member one time.

1. If the family has more than one child enrolled in the TEDDY study and a family ID has already been assigned to one of the TEDDY children (family ID is automatically assigned by the DCC at the time of the first save of any of the family member SCFs), enter that family ID in the corresponding field on one of the family member's SCFs, that samples have been collected from, for the other TEDDY subject(s) that have not yet been associated with this family ID. This family ID will automatically prepopulate on all of the other family member SCFs for this subject. At analysis time, this will allow the DCC to know that the children are related and that the family member's sample information can also be associated with this TEDDY subject.
2. If the family has more than one child enrolled in the TEDDY study and a relative ID has already been assigned to that family member (relative ID is automatically assigned by the DCC), enter that relative ID in the corresponding field on the other TEDDY subject's relative's SCF. For example if Subject A and Subject B are full siblings, both enrolled in the TEDDY Study and their biological mother has been assigned Relative ID 12345 on the Mother's DNA SCF associated with Subject A, site would enter Relative ID 12345 on the Mother's DNA SCF associated with Subject B.
3. If the specific family member's sample information and answers to questions at the bottom of the form have already been entered on the other subject's family member SCF then this information does not need to be re-entered on this TEDDY subject's family member SCF. All that must be entered is the family ID on the first save of the first family member's SCF and the corresponding relative ID on each family member's SCF.

   NOTE: If there is more than one child from one family enrolled in TEDDY, the non-HLA genotyping sample can be used as the sibling DNA sample (a new blood sample does not need to be collected for the sibling DNA sample). The DCC is currently working on a way to link this data and will send an announcement to sites once the system has been altered to link the data.

   NOTE: Once you save a SCF with only the family ID and Relative ID entered, you will not be able to make any changes to the SCF. If you need a correction made, please contact the DCC.

4. If the specific family member's sample information and answers to questions at the bottom of the form have NOT been entered on the other subject's family member SCF, then enter the information on this subject's family member SCF and if the family member ID has not yet been prepopulated on the form also enter it and enter the corresponding relative ID of the family member.
5. Click the save button and close the form.
6. Repeat this as necessary for each family member that samples have been collected from.

Once the Participant's Details Page has been refreshed, you will see "Biological Father's DNA Sample Collection Form", "Biological Mother's DNA Sample Collection Form" or "Sibling's DNA Sample Collection Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1. Click on the form link under 'Completed Additional Study Forms'
2. A new window will open which will have a link to the form that has been saved for this subject.
3. Click on the 'View/Edit/Print" link to open up the specific form for this subject.

<u>Tracking System instructions for parent and sibling DNA samples and antibody samples</u>

If the site is unable to collect both a DNA sample and antibody sample from a parent or sibling, the site should mark a not done reason in the tracking system of the SCF:

1. Go to the corresponding Sample Collection Form:
    a. These SCFs can be found under the Additional Study Forms drop-down menu at the upper right-hand corner of the Participant's Details Page – you will find a separate form for each relative: "Biological Father's DNA Sample Collection Form", "Biological Mother's DNA Sample Collection Form" and "Sibling's DNA Sample Collection Form" (if the TEDDY subject has multiple siblings, choose a new sibling SCF for each sibling).
    b. Choose the desired form and click the "Select Form" button that is below the dropdown menu.
2. Select "Tracking System" button at top of SCF.
3. A new window will open which allows the site to enter the reason why the samples were not collected.
4. Once the not done reason has been selected, click "Save Form".

Once the Participant's Details Page has been refreshed, you will see "Biological Father's DNA Sample Collection Form", "Biological Mother's DNA Sample Collection Form" or "Sibling's DNA Sample Collection Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1. Click on the form link under 'Completed Additional Study Forms'
2. A new window will open which will have a link to the tracking system form that has been saved for this subject.
3. Click on the 'Tracking' link to open up the specific tracking system form for this subject.

17.2.21. Instructions for using the Post-Diagnosis Visit MMTT Sample Collection Form

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject
4. Under "Search Results", click on the Local Code of the desired subject.
5. The site should choose "Post-Diagnosis Visit MMTT Sample Collection Form" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
6. Click 'Select Form' button that is below dropdown menu.
7. Enter information (see MOO section 13.7 for detailed instructions on MMTTs and entering data on the MMTT Sample Collection Form), click the Save button and close the form.

Once the Participant's Details Page has been refreshed, you will see "Post-Diagnosis Visit MMTT Sample Collection Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1. Click on the form link under 'Completed Additional Study Forms'
2. A new window will open which will have a link to the "Post-Diagnosis Visit MMTT Sample Collection Form" that has been saved for this subject.
3. Click on the 'View/Edit/Print" link to open up the specific form for this subject.

Tracking System instructions for MMTT Samples

If the site is unable to collect data for the form, the site should mark a not done reason in the tracking system of the form:

1. Go to the corresponding form:

   a. Choose "Post-Diagnosis Visit MMTT Sample Collection Form" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
   b. Click 'Select Form' button that is below dropdown menu.
2. Select "Tracking System" button at top of form.
3. A new window will open which allows the site to enter the reason why the form was not completed.
4. Once the not done reason has been selected, click "Save Form".

Once the Participant's Details Page has been refreshed, you will see "Post-Diagnosis Visit MMTT Sample Collection Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1. Click on the form link under 'Completed Additional Study Forms'
2. A new window will open which will have a link to the tracking system form that has been saved for this subject.

Click on the 'Tracking' link to open up the specific tracking system form for this subject.

17.2.22. Instructions for using the Post-Diagnosis Visit MMTT Procedure Form

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject
4. Under "Search Results", click on the Local Code of the desired subject.
5. The site should choose "Post-Diagnosis Visit MMTT Procedure Form" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
6. Click 'Select Form' button that is below dropdown menu.
7. Enter information, click the Save button and close the form.

Once the Participant's Details Page has been refreshed, you will see "Post-Diagnosis Visit MMTT Procedure Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1. Click on the form link under 'Completed Additional Study Forms'
2. A new window will open which will have a link to the "Post-Diagnosis Visit MMTT Procedure Form" that has been saved for this subject.
3. Click on the 'View/Edit/Print" link to open up the specific form for this subject.

Tracking System instructions for MMTT Procedure Form

If the site is unable to collect data for the form, the site should mark a not done reason in the tracking system of the form:

1. Go to the corresponding form:
    a. Choose "Post-Diagnosis Visit MMTT Procedure Form" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
    b. Click 'Select Form' button that is below dropdown menu.
2. Select "Tracking System" button at top of form.
3. A new window will open which allows the site to enter the reason why the form was not completed.
4. Once the not done reason has been selected, click "Save Form".

Once the Participant's Details Page has been refreshed, you will see "Post-Diagnosis Visit MMTT Procedure Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1. Click on the form link under 'Completed Additional Study Forms'
2. A new window will open which will have a link to the tracking system form that has been saved for this subject.
3. Click on the 'Tracking' link to open up the specific tracking system form for this subject.

17.2.23. Instructions for using the Post-Diagnosis Visit Diabetes Management Form

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject
4. Under "Search Results", click on the Local Code of the desired subject.
5. The site should choose "Post-Diagnosis Visit Diabetes Management Form" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
6. Click 'Select Form' button that is below dropdown menu.
7. Enter information, click the Save button and close the form.

Once the Participant's Details Page has been refreshed, you will see "Post-Diagnosis Visit Diabetes Management Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1. Click on the form link under 'Completed Additional Study Forms'
2. A new window will open which will have a link to the "Post-Diagnosis Visit Diabetes Management Form" that has been saved for this subject.

3. Click on the 'View/Edit/Print" link to open up the specific form for this subject.

Tracking System instructions for Diabetes Management Form

If the site is unable to collect data for the form, the site should mark a not done reason in the tracking system of the form:

1. Go to the corresponding form:
    a. Choose "Post-Diagnosis Visit Diabetes Management Form" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
    b. Click 'Select Form' button that is below dropdown menu.
2. Select "Tracking System" button at top of form.
3. A new window will open which allows the site to enter the reason why the form was not completed.
4. Once the not done reason has been selected, click "Save Form".

Once the Participant's Details Page has been refreshed, you will see "Post-Diagnosis Visit Diabetes Management Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1. Click on the form link under 'Completed Additional Study Forms'
2. A new window will open which will have a link to the tracking system form that has been saved for this subject.
3. Click on the 'Tracking' link to open up the specific tracking system form for this subject.

17.2.24. Instructions for using the Retention Efforts Tracking Form

The form is designed to be completed at the visit after the Junior Scientist book was given. The form will include the following:

First Junior Scientist book:
If book will not be given to family, mark provided check box.
1. Date family was given book
2. Ask parents: "Have you read the Junior Scientist book with/for your child?" (response format: Yes/No) - If the parent answers "yes" to this item, item 3 will automatically be grayed out.
3. Ask parents: "Have you read the Junior Scientist book with/for your child?" (response format: Yes/No) - This question is for the next visit and only asked if the parent stated "no" to item 2 which was asked at the preceding visit. If the parent again answers "no", they will not be asked this question again.

NOTE: If the parent is asked item 3 at the next visit, the answer should be indicated on the same previously submitted "Retention Efforts Tracking" form, not on a new form

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject
4. Under "Search Results", click on the Local Code of the desired subject.
5. The site should choose "Retention Efforts Tracking" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
6. Click 'Select Form' button that is below dropdown menu.
7. Enter information, click the Save button and close the form.

Once the Participant's Details Page has been refreshed, you will see "Retention Efforts Tracking" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1. Click on the form link under 'Completed Additional Study Forms'
2. A new window will open which will have a link to the "Retention Efforts Tracking" that has been saved for this subject.
3. Click on the 'View/Edit/Print" link to open up the specific form for this subject.

17.2.25. Instructions for using Whole Genome Sequencing Information Form

This form should be used to indicate if informed consent has been given for Whole Genome Sequencing on the subject's and/or parent's sample(s) and if applicable to the site if the subject and/or parent would like to receive the results or not. There are two sections to the form 1) Whole Genome Sequencing Subject Information and 2) Whole Genome Sequencing Parent Information.

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject
4. Under "Search Results", click on the Local Code of the desired subject.
5. The site should choose "Whole Genome Sequencing Information Form" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
6. Click 'Select Form' button that is below dropdown menu.

7. Enter information, click the Save button and close the form.

Once the Participant's Details Page has been refreshed, you will see "Whole Genome Sequencing Information Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1. Click on the form link under 'Completed Additional Study Forms'
2. A new window will open which will have a link to the "Whole Genome Sequencing Information Form" that has been saved for this subject.
3. Click on the 'View/Edit/Print" link to open up the specific form for this subject.

17.2.26. Instructions for using Primary Tooth Sample Collection Form

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject
4. Under "Search Results", click on the Local Code of the desired subject.
5. The site should choose "Primary Tooth Sample Collection Form" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
6. Click 'Select Form' button that is below dropdown menu.
7. Enter information (see MOO section 13 for detailed instructions on primary tooth collection and entering data on the Primary Tooth Sample Collection Form), click the Save button and close the form.

Once the Participant's Details Page has been refreshed, you will see "Primary Tooth Sample Collection Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1. Click on the form link under 'Completed Additional Study Forms'
2. A new window will open which will have a link to the "Primary Tooth Sample Collection Form" that has been saved for this subject.
3. Click on the 'View/Edit/Print" link to open up the specific form for this subject.

17.2.27. Instructions for using Additional Serum Sample for Subjects First Autoantibody Positive at 15 Year Visit Sample Collection Form

Some TEDDY subjects have been deemed islet autoantibody positive for the first time at their 15 year visit, which is the last TEDDY visit. TEDDY is unable to determine autoantibody persistence for these subjects since there are no more scheduled TEDDY visits. Some of these subjects

participate in follow-up studies in which a serum sample is collected after their participation in TEDDY. The "Additional Serum Sample for Subjects First Autoantibody Positive at 15 Year Visit Sample Collection Form" should be used for this sample so that it can also be tested in the TEDDY autoantibody reference lab(s). A TEDDY vial barcode sticker received from the DCC should be used for these samples in order to ensure that the vial number does not conflict with TEDDY samples.

1. Logon to the TEDDY website http://teddy.epi.usf.edu/
2. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
3. Search for the desired subject
4. Under "Search Results", click on the Local Code of the desired subject.
5. The site should choose "Additional Serum Sample for Subjects First Autoantibody Positive at 15 Year Visit Sample Collection Form" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
6. Click 'Select Form' button that is below dropdown menu.
7. Enter information (see MOO section 14 for detailed instructions on serum sample collection and entering data on the Serum Sample Collection Form), click the Save button and close the form.

Once the Participant's Details Page has been refreshed, you will see "Additional Serum Sample for Subjects First Autoantibody Positive at 15 Year Visit Sample Collection Form" under 'Completed Additional Study Forms' near top of Participant's Details Page:

1. Click on the form link under 'Completed Additional Study Forms'
2. A new window will open which will have a link to the "Additional Serum Sample for Subjects First Autoantibody Positive at 15 Year Visit Sample Collection Form" that has been saved for this subject.
3. Click on the 'View/Edit/Print" link to open up the specific form for this subject.

17.3.Dietary Data

17.3.1. File Naming Schema

For all TEDDY dietary files sent to the DCC, the following naming scheme is used:

TD101_04NOV

Where:

TD= A constant (Teddy Diet)

106 = visit location code

(example 106 is TEDDY/DAISY Clinic in Colorado)

04 = year

NOV= month

This naming scheme should correspond to the project name for those sites that submit a project name. For US sites, the zip files generated by NDS-R need to renamed at the time of creation accordingly. For sites that need to send multiple files each month, the designation _1 or _2 is to be added to the name (i.e. TD101_04NOV_1). For any revised files, due to new foods or other file modifications at the clincal sites, the designation _REV is to be added to the name (i.e. TD101_04NOV_REV). This will indicate to the DCC that this file was previously received and has been revised.

All TEDDY diet record files should be sent as .CSV, .xls, or .sas7bdat, except for files from the USA, where the obligatory file extension .zip is generated by NDS-R. If the files are sent in these formats then the DCC will be able to process European method of recording dates and the use of commas, "," instead of decimal points, "." in the decimal values.

17.3.2. Submitting Dietary Data Files

1) To submit dietary data files to the DCC, first login to the TEDDY Members website.
2) Click on 'Data Upload' under the 'Data Management' heading of the left navigation menu.
3) To upload the dietary data files from your database, click the 'Browse…' button on the data upload page. This will give you a standard windows type explorer so you can find the files you wish to submit. Once you have found the file, click 'Open'.
4) Click 'Upload' to send the selected file to the DCC.
5) Once your submission is final you will see the name, upload status, and upload date/time of your file in the recent uploaded files list on this page.

17.4.Events Not Submitted Report

The Events Not Submitted Report (III.07) can be found on the TEDDY website under each Clinical Center's Report section. This report lists all items (forms, diet records, samples) that are expected to be submitted/collected by this point in time, but for which the DCC has received no information.

- An expected date is calculated for each visit based upon the baby's birth date (so for example a baby's 9 month visit has an expected date of 9 months from the baby's DOB). From this expected date we give 30 days lag time for questionnaires associated with that particular visit, 60 days lag time for blood, water, toenail samples and 3 day diet records associated with that particular visit, and 90 days lag time for stool samples associated with that particular visit before they appear on the Events Not Submitted Report.

- You must submit information for the item through the questionnaire or SCF or use the tracking system to indicate a 'not done' reason in order for the item not to appear on the report anymore.
- When a subject has withdrawn, is lost to follow-up or has been diagnosed with diabetes:
  - if withdraw, LTF or diagnosis date occurs after a visit's expected date, then that visit's questionnaires & samples are expected and will show up on the Events Not Submitted Report (after the appropriate amount of lag time) if no information has been submitted to the DCC.
  - You must submit information for the item through the questionnaire or SCF or use the tracking system to indicate a 'not done' reason in order for the item not to appear on the report anymore.

17.5. Instructions for using the TEDDY website Calendars

17.5.1. The TEDDY Calendar

1) This calendar is available for all TEDDY website members to announce events relevant to the TEDDY study such as meetings, conference calls, etc.
2) To view this calendar, click on the calendar icon directly below the announcements on the Home page of the TEDDY member's website.
3) To move between months of the calendar year, click the < and > symbols to move back a month and forward a month respectively.
4) To view an appointment in detail, click on the appointment name.
5) To add the appointment to your personal Outlook calendar, click 'Add to Outlook Calendar'.
6) To close the appointment details or go back to the calendar, click 'Back To Calendar'.
7) To add an appointment, click on the day of the event, then click the 'Add Appointment' button. Fill in the details of the appointment and click the 'Submit' button.

17.5.2. Committee Calendars

1) This calendar is available for the members of each committee to announce events relevant to that committee such as meetings, conference calls, etc.
2) To view this calendar, click on the name of the committee on the left menu. Then click the calendar icon directly below the Committee name.
3) To move between months of the calendar year, click the < and > symbols to move back a month and forward a month respectively.
4) To view an appointment in detail, click on the appointment name.
5) To add the appointment to your personal Outlook calendar, click 'Add to Outlook Calendar'.
6) To close the appointment details or go back to the calendar, click 'Back To Calendar'.
7) To add an appointment, click on the day of the event, then click the 'Add Appointment' button. Fill in the details of the appointment and click the 'Submit' button.

17.6. Giving TEDDY staff members access to subject information (based upon Visit Location Code)

The DCC will grant certain staff members (as requested by clinical center) at each site the ability to give staff members at their site access to subject information (based upon Visit Location Code). If you have been granted this permission by the DCC follow the instructions below to give staff members at your site access to subject information:

1) Click on 'Member Directory' at the top of the webpage.
2) Search for the desired user
3) Scroll to the bottom of the screen and you will see Institution Access:
   For your institution you will see that there is a clinical center row (GEO, COL, WAS, FIN, SWE, or GER) as well as rows for each of the different visit locations associated with this clinical center. You have to choose the clinical center option and whatever visit locations you want the person to have access to (you need to mark these rows by choosing options from the headings, see below).
4) You will see 7 headings of choices:
   1) No Access - this user cannot view or change data, add/edit announcements, nor add/edit folders and files, for the given Institutions.
   2) Read Access - the user can view data, folders, files and announcements, but not add or change data, files, folders, or announcements for the given Institutions (unless Group Security is turned on for specific folders).
   3) Write Access - the new user can view, add, and edit data, files, folders and announcements for the given Institutions (unless Group Security is turned on for specific folders).
   4) Add/Edit user – this will allow the new user to add and edit user permissions for the given Institution; only DCC can grant access – please contact the DCC about people you would like to be able to add/edit users for this new visit location.
   5) Group Admin – this will allow the new user to create and manage groups for document security (for more information on group security, see Group Security); only DCC can grant access.
   6) HLA Result Emails - user will receive HLA screening result emails for given locations; only DCC can grant access – please contact the DCC about people that you would like to receive HLA results for this new visit location code.
   7) Compliance Emails - user will receive compliance reports (IRB expiration, Incomplete enrollment forms, Incomplete screening forms, etc)
   8) Click Save at bottom of screen

17.7. Data Collection During COVID-19

See documentation saved here on TEDDY members' website: https://teddy.epi.usf.edu/webapp/MainPage.aspx?DirectoryOwnerId=2885&Root=0&Owner=1000

18 TEDDY Reimbursement System

All samples must be drawn within the corresponding visit window and only one sample per visit window will be reimbursed unless otherwise specified below.

18.1 HLA Screening Sample

- $35 for blood sample collection for all samples collected prior to September 1, 2008
- $36.05 for blood sample collection for all samples collected on or after September 1, 2008
- $20 for local lab typing for all samples typed prior to September 1, 2008
- $20.60 for local lab typing for all samples typed on or after September 1, 2008
- Not reimbursable for the following circumstances
    - Subject is older than 4 months of age
    - Sample is deemed unusable (see attached list for unusable reasons)

18.2 HLA Confirmation Sample

- $91 per sample to the HLA Reference Laboratory
    - To be paid once the samples are run by the lab and the results are received by the DCC.

18.3 Clinic Visit Blood Draws

- $50 for any amount of blood drawn prior to September 1, 2008; $51.50 for any amount of blood drawn on or after September 1, 2008 – includes the following tests
    - HLA confirmation
    - Plasma
    - mRNA
    - Autoantibodies
    - Autoantibodies – QC and confirmation
    - Serum cytokines and markers of inflammation
    - Transglutaminase antibodies
    - Thyroid
    - Enterovirus
    - Rotavirus
    - Bacteria
    - 25, hydroxyvitamin D
    - Erythrocyte membrane fatty acid
    - Alpha-tocopherol, gamma-tocopherol
    - Carotenoids
    - Ascorbic acid
    - Buffy Coat (or PBMC on selected subjects)
    - HbA1c
    - Non-HLA genotyping sample

- $50 for Maternal Autoantibody sample drawn prior to September 1, 2008; $51.50 for Maternal Autoantibody sample drawn on or after September 1, 2008
- Not reimbursable for the following circumstances
    - Sample is drawn outside the corresponding visit window
    - If they have **no** usable sample from blood draw
    - Sample is deemed unusable (see attached list for unusable reasons)

18.4 Questionnaires

- $100 per clinic visit for all **completed** questionnaires at that visit collected prior to September 1, 2008; $103 per clinic visit for all **completed** questionnaires at that visit collected on or after September 1, 2008
- Completed questionnaires will be defined by required fields. These fields were chosen for their importance in data collection relevant to the study outcomes.
- All of the required questionnaires must be completed within the appropriate visit window.
- Only the questionnaires listed below will be counted for reimbursement.

3 Month Visit

First Questionnaire

- The DCC must receive one of the following complete forms: Mother, Father, or primary caretaker
- The completed date for the questionnaire must fall within the visit window
- Fields required for completeness
    - Mother – 1-12, 14
    - Father – at least one question, any question
    - Primary Caretaker – 2 and 3

3 Month Interview

- The interview date must fall within the visit window
- Fields required for completeness – 6, 9-12, 15-18

6 Month Visit

6 Month Questionnaire

- The DCC must receive a complete form from either the Mother, Father, or primary caretaker
- The completed date must fall within the visit window
- Fields required for completeness – 7, 9, 10

TEDDY Book Extraction

- The interview date must fall within the visit window
- Fields required for completeness – 1-4, and any part of 6

9 Month Visit
9 Month Interview
- The completed date must fall within the visit window
- Fields required for completeness – 12-14

Family History Questionnaire
- Fields required for completeness – at least one question, any question

TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-4, and any part of 6

12 Month Visit
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-4, and any part of 6

15 Month Visit
Annual Questionnaire
- The completed date must fall within the visit window
- Fields required for completeness – 9 and 10

TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-4, and any part of 6

18 Month Visit
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-4, and any part of 6

21 Month Visit
Update Form for Primary Caretaker Interview
- The completed date must fall within the visit window
- Fields required for completeness – 12-14

TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-4, and any part of 6

24 Month Visit
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-4, and any part of 6

27 Month Visit
Annual Questionnaire
- The completed date must fall within the visit window
- Fields required for completeness – 9 and 10

TEDDY Book Extraction (2-5 years old book starts being used at this visit)
- The interview date must fall within the visit window
- Fields required for completeness – 1-3, and any part of 5

30 Month Visit
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-3, and any part of 5

33 Month Visit
Update Form for Primary Caretaker Interview
- The completed date must fall within the visit window
- Fields required for completeness – 12-14

Update Form for Family History Questionnaire
- Fields required for completeness – at least one question, any question

TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-3, and any part of 5

36 Month Visit
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-3, and any part of 5

39 Month Visit
Annual Questionnaire
- The completed date must fall within the visit window
- Fields required for completeness – 9 and 10

TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-3, and any part of 5

42 Month Visit
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-3, and any part of 5

45 Month Visit
Update Form for Primary Caretaker Interview
- The completed date must fall within the visit window
- Fields required for completeness – 12-14

TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-3, and any part of 5

48 Month Visit
Annual Questionnaire
- The completed date must fall within the visit window
- Fields required for completeness – 9 and 10

TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-3, and any part of 5

51 Month Visit#
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-3, and any part of 5

54 Month Visit
Update Form for Primary Caretaker Interview
- The completed date must fall within the visit window
- Fields required for completeness – 12-14

Update Form for Family History Questionnaire
- Fields required for completeness – at least one question, any question

TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-3, and any part of 5

57 Month Visit#
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-3, and any part of 5

5 Year Visit – As of October 19, 2015 only one of the following (Annual Questionnaire OR TEDDY Book Extraction) must be completed for the full questionnaire reimbursement at the 5 Year Visit
Annual Questionnaire
- The completed date must fall within the visit window

- Fields required for completeness – 9 and 10

TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-3, and any part of 5

5 Year 3 Month Visit#
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-3, and any part of 5

5 Year 6 Month Visit
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-3, and any part of 5

5 Year 9 Month Visit#
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-3, and any part of 5

6 Year Visit – As of October 19, 2015 only one of the following (Annual Questionnaire OR TEDDY Book Extraction) must be completed for the full questionnaire reimbursement at the 6 Year Visit
Annual Questionnaire
- The completed date must fall within the visit window
- Fields required for completeness – 9 and 10

TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-3, and any part of 5

6 Year 3 Month Visit#
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

6 Year 6 Month Visit
Update Form for Primary Caretaker Interview
- The completed date must fall within the visit window
- Fields required for completeness – 12-14

TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

6 Year 9 Month Visit#
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

7 Year Visit – As of October 19, 2015 only one of the following (Annual Questionnaire OR TEDDY Book Extraction) must be completed for the full questionnaire reimbursement at the 7 Year Visit
Annual Questionnaire
- The completed date must fall within the visit window
- Fields required for completeness – 9 and 10

TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

7 Year 3 Month Visit#
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

7 Year 6 Month Visit
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

7 Year 9 Month Visit#
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

8 Year Visit – As of October 19, 2015 only one of the following (Annual Questionnaire OR TEDDY Book Extraction) must be completed for the full questionnaire reimbursement at the 8 Year Visit
Annual Questionnaire
- The completed date must fall within the visit window
- Fields required for completeness – 9 and 10

TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

8 Year 3 Month Visit#
TEDDY Book Extraction

- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

8 Year 6 Month Visit
Update Form for Primary Caretaker Interview
- The completed date must fall within the visit window
- Fields required for completeness – 12-14

Update Form for Family History Questionnaire
- Fields required for completeness – at least one question, any question

TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

8 Year 9 Month Visit#
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

9 Year Visit – As of October 19, 2015 only one of the following (Annual Questionnaire OR TEDDY Book Extraction) must be completed for the full questionnaire reimbursement at the 9 Year Visit
Annual Questionnaire
- The completed date must fall within the visit window
- Fields required for completeness – 9 and 10

TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

9 Year 3 Month Visit#
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

9 Year 6 Month Visit
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

9 Year 9 Month Visit#
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

10 Year Visit – As of October 19, 2015 only one of the following (Annual Questionnaire OR TEDDY Book Extraction) must be completed for the full questionnaire reimbursement at the 10 Year Visit

Annual Questionnaire

- The completed date must fall within the visit window
- Fields required for completeness – 9 and 10

TEDDY Book Extraction

- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

10 Year 3 Month Visit#

TEDDY Book Extraction

- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

10 Year 6 Month Visit

Update Form for Primary Caretaker Interview

- The completed date must fall within the visit window
- Fields required for completeness – 12-14

TEDDY Book Extraction

- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

10 Year 9 Month Visit#

TEDDY Book Extraction

- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

11 Year Visit – As of October 19, 2015 only one of the following (Annual Questionnaire OR TEDDY Book Extraction) must be completed for the full questionnaire reimbursement at the 11 Year Visit

Annual Questionnaire

- The completed date must fall within the visit window
- Fields required for completeness – 9 and 10

TEDDY Book Extraction

- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

11 Year 3 Month Visit#

TEDDY Book Extraction

- The interview date must fall within the visit window

- Fields required for completeness – 1-2, and any part of 4

11 Year 6 Month Visit
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

11 Year 9 Month Visit#
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

12 Year Visit – As of October 19, 2015 only one of the following (Annual Questionnaire OR TEDDY Book Extraction) must be completed for the full questionnaire reimbursement at the 12 Year Visit
Annual Questionnaire
- The completed date must fall within the visit window
- Fields required for completeness – 9 and 10

TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

12 Year 3 Month Visit#
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

12 Year 6 Month Visit
Update Form for Primary Caretaker Interview
- The completed date must fall within the visit window
- Fields required for completeness – 12-14

Update Form for Family History Questionnaire
- Fields required for completeness – at least one question, any question

TEDDY Book Extraction
- The interview date must fall within the visit window
  Fields required for completeness – 1-2, and any part of 4

12 Year 9 Month Visit#
TEDDY Book Extraction
- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

13 Year Visit – As of October 19, 2015 only one of the following (Annual Questionnaire OR TEDDY Book Extraction) must be completed for the full questionnaire reimbursement at the 13 Year Visit

Annual Questionnaire

- The completed date must fall within the visit window
  Fields required for completeness – 9 and 10

TEDDY Book Extraction

- The interview date must fall within the visit window
  Fields required for completeness – 1-2, and any part of 4

13 Year 3 Month Visit#

TEDDY Book Extraction

- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

13 Year 6 Month Visit

TEDDY Book Extraction

- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

13 Year 9 Month Visit#

TEDDY Book Extraction

- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

14 Year Visit – As of October 19, 2015 only one of the following (Annual Questionnaire OR TEDDY Book Extraction) must be completed for the full questionnaire reimbursement at the 14 Year Visit

Annual Questionnaire

- The completed date must fall within the visit window
- Fields required for completeness – 9 and 10

TEDDY Book Extraction

- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

14 Year 3 Month Visit#

TEDDY Book Extraction

- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

14 Year 6 Month Visit
Update Form for Primary Caretaker Interview

- The completed date must fall within the visit window
- Fields required for completeness – 12-14

TEDDY Book Extraction

- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

14 Year 9 Month Visit#
TEDDY Book Extraction

- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

15 Year Visit – As of October 19, 2015 only one of the following (End of TEDDY Parent Questionnaire OR TEDDY Book Extraction) must be completed for the full questionnaire reimbursement at the 15 Year Visit
End of TEDDY Parent Questionnaire

- The completed date must fall within the visit window
- Fields required for completeness – 20

TEDDY Book Extraction

- The interview date must fall within the visit window
- Fields required for completeness – 1-2, and any part of 4

= Children four years of age and older who have been deemed persistent autoantibody positive will remain on the 3 month visit schedule (confirmation results from the confirmatory Autoantibody lab will not be taken into consideration for determining the subject's visit schedule, only the local lab's results will be used for this); all other subjects will attend clinic visits every 6 months beginning at 4 years of age until age 15. For subjects who become autoantibody positive at 4 years of age or older, the subject will be reinstated on the three month visit schedule at the first indication of autoantibody positivity and will stay on if persistent. If the next available sample is negative, thus the subject is not deemed persistent autoantibody positive, the subject will be seen every six months instead of every three months from that point on. Subjects who have been persistently autoantibody positive, but who become negative to all antibodies for 1 year or more will be placed on the biannual visit schedule after 4 years of age.

- All questionnaires listed for each time period must be completed in order for reimbursement.
- If a patient misses a visit then the questionnaires can be mailed or interviews done by phone.

18.5 First Child Questionnaire

- $10 will be reimbursed for each First Child Questionnaire submitted
- The completed date must fall within the visit window

- Fields required for completeness – 7-8

18.6 Annual Child Questionnaire

- $10 will be reimbursed for each Annual Child Questionnaire submitted
- The completed date must fall within the visit window
- Fields required for completeness – 4-5

18.7 End of TEDDY Child Questionnaire

- $10 will be reimbursed for the End of TEDDY Child Questionnaire submitted at the 15 year visit
- The completed date must fall within the visit window
- Fields required for completeness – 12

18.8 Strengths and Difficulties Questionnaire (SDQ)

- $10 will be reimbursed for a SDQ submitted at the 11 year 6 month visit
- $10 will be reimbursed for a SDQ submitted at the 13 year 6 month visit
- Sites will not be reimbursed for each SDQ completed at a visit should both the child and parent(s) complete a SDQ
- The completed date must fall within the visit window
- All questions must be answered to make the form complete

18.9 Post-diagnosis Visit Quality of Life Questionnaires

- $50 for all **completed** Quality of Life Questionnaires at the post-diagnosis visit
- Only the questionnaires listed below will be counted for reimbursement.

PEDsQL for parents

- Fields required for completeness – at least 50% of all questions on the form must be answered
- The DCC must receive a complete form from either the Mother, Father, or primary caretaker

PEDsQL for children (if child is at least 8 years old)

- Fields required for completeness – at least 50% of all questions on the form must be answered

STAI and Well-being question for parents

- Fields required for completeness – all questions must be answered
- The DCC must receive a complete form from either the Mother, Father, or primary caretaker

STAI for children (if child is at least 8 years old)

- Fields required for completeness – all questions must be answered

PIP

- Fields required for completeness – at least 90% of all items on the form (this means 90% of answers in both categories "how often?" and "how difficult?" and not 90% of each scale) must be answered
- The DCC must receive a complete form from either the Mother, Father, or primary caretaker

18.10 24 Hour Recalls and 3 Day Diet Records

- $25 will be reimbursed for each 24 hour recall submitted on or after September 1, 2008
- $75 will be reimbursed for each 3 day diet record submitted on or after September 1, 2008
    - NOTE: In August 2018, the collection protocol was changed so as to continue to collect 3 day diet records every 6 months from subjects who are single or multiple persistent confirmed autoantibody positive (even if the subject reverts to autoantibody negativity) and to stop 3 day diet record collections on all other subjects after the 10 year visit. Should a subject be deemed single or multiple persistent confirmed autoantibody positive after the 10 year visit, the 3 day diet record collection will be restarted at the next visit.
    - NOTE: In 2020, it was decided that ALL 3 day diet record collections on ALL subjects would stop April 1, 2020.
- Recall or record must be completed within the appropriate visit window.

18.11 Patient Incentives

- $300 per year ($75/quarter when subject is on 3 month visit schedule; $150 biannually when subject is on 6 month visit schedule) prior to September 1, 2008; $309 per year ($77.25/quarter when subject is on 3 month visit schedule; $154.50 biannually when subject is on 6 month visit schedule) for September 1, 2008 – May 31, 2012; $400 per year ($100/quarter when subject is on 3 month visit schedule; $200 biannually when subject is on 6 month visit schedule) on or after June 1, 2012
- Money will be disbursed quarterly (when subject on 3 month visit schedule) and biannually (when subject on 6 month visit schedule) based on the following criteria:
    - any **completed** questionnaire or **usable** sample done in that quarter
    - even if patient misses visit but mails questionnaires or samples

18.12 Water Sample

- $10 for samples collected prior to September 1, 2008 and $10.30 for samples collected on or after September 1, 2008, at 9 month visit (12 month if not able to get at 9 month), once it reaches the repository (in order to be reimbursed a minimum of 3 cryovials, filled to the fill line, must be receipted by the repository)
- $10 for samples collected prior to September 1, 2008 and $10.30 for samples collected on or after September 1, 2008, for water samples to be collected every 2 years at the annual visit (or the next visit in the visit schedule if not

able to get at the annual visit) for ages 3, 5, 7, etc. through the life of the study, once it reaches the repository (in order to be reimbursed up until March 1, 2019 a minimum of 3 cryovials, filled to the fill line, must be receipted by the repository; from March 1, 2019 and on a minimum of 2 cryovials, filled to the fill line, must be receipted by the repository)

- Not reimbursable for the following circumstances
  - Sample is deemed unusable (see attached list for unusable reasons)
  - Sample is collected outside the corresponding visit window

18.13 Stool Samples

- $10 for samples collected prior to September 1, 2008 and $10.30 for samples collected on or after September 1, 2008, for each sample, once it reaches the repository
  - NOTE: In August 2018 all stool sample collections were stopped on all subjects.
- Not reimbursable for the following circumstances
  - Sample is deemed unusable (see attached list for unusable reasons)
  - Sample is collected outside the corresponding visit window

18.14 Toenail Sample

- $10 for samples collected prior to September 1, 2008 and $10.30 for samples collected on or after September 1, 2008, for each sample, once it reaches the repository
- Not reimbursable for the following circumstances
  - Sample is deemed unusable (see attached list for unusable reasons)
  - Sample is collected outside the corresponding visit window

18.15 Nasal Swab Sample

- $10.30 for each sample, once it reaches the repository
- Not reimbursable for the following circumstances
  - Sample is deemed unusable (see attached list for unusable reasons)
  - Sample is collected outside the corresponding visit window

18.16 Salivary Cortisol Sample

- $10.30 for each sample, once it reaches the lab or repository
- Not reimbursable for the following circumstances
  - Sample is deemed unusable (see attached list for unusable reasons)
  - Sample is collected outside the corresponding visit window

18.17 OGTT

- $150 for two time-point OGTTs completed prior to September 1, 2008 and $154.50 for two time-point OGTTs completed on or after September 1, 2008 and $220 for six time-point OGTTs - to be performed every six months on every child who has tested positive for two or more autoantibodies, regardless of autoantibody positivity confirmation or persistence, at any previous visit

(but both antibodies must be positive at the same visit) and who is three years of age or older
  - Will not reimburse for OGTT's done outside this protocol
  - For two time-point OGTTs: Both 0 minute glucose reading and 120 minute glucose reading are required for reimbursement
  - For six time-point OGTTs: Collection of all six time-point glucose samples are required for reimbursement

18.18 MMTT

- $154.50 for each MMTT
  - Will not reimburse for MMTT's done outside of protocol.
  - -10 minutes and 120 minutes glucose readings are required for reimbursement

18.19 Parent/Sibling DNA Sample

- $15 for each sample, once it reaches the lab (only one sample will be reimbursed per family member)
- Not reimbursable for the following circumstances
  - Sample is deemed unusable (see attached list for unusable reasons)

18.20 Urine Sample

- $15 for each sample, once it reaches the repository
- Not reimbursable for the following circumstances
  - Sample is deemed unusable (see attached list for unusable reasons)
  - Sample is collected outside the corresponding visit window

18.21 TEDDY Update Form

- $10 per completed form with successful contact made

18.22 Physical Activity Assessment

- $35 per completed physical activity assessment
  - NOTE: In August 2018, the collection protocol was changed so as to continue to collect physical activity assessments annually from subjects who are single or multiple persistent confirmed autoantibody positive (even if the subject reverts to autoantibody negativity) and to stop physical activity assessments on all other subjects after the 10 year visit. Should a subject be deemed single or multiple persistent confirmed autoantibody positive after the 10 year visit, the physical activity assessment will be restarted at the next visit.
- An Activity Log Consolidation Form and Activity Monitor Data Upload must both be submitted
- The Activity Log Consolidation Form and Activity Monitor Data Upload must be completed within the appropriate visit window

18.23 Whole Genome Sequencing Consent

- $50 per consent ('Yes', 'Yes, by waiver of consent' or 'No' to question #1 on the Whole Genome Sequencing Subject Information Form)

18.24 Reimbursement for Subjects Deemed "Ineligible" from the 9 Month HLA Confirmation Test

- For subjects who are initially determined to be HLA eligible by the local clinical screening lab, but are then determined to be HLA ineligible from the 9 month HLA sample by the HLA Reference lab, the family is given the option of whether to continue in the study or not.
    - If the family decided to continue in the study the clinical centers will be reimbursed for completed questionnaire, usable samples, and patient incentives following the rules outlined above.
- Local screening laboratories are only allowed to have a 2% error rate in the determination of HLA eligibility. If the error rate ever goes above 2%, disciplinary actions will be taken and the clinical center may not continue to be reimbursed for these subjects.

Table 18.1 Reasons for Samples to be Declared Unusable

Sample Status	Interpretation	Usable
9901	Sample not received	No
9902	Sample lost during processing	No
9903	Delayed arrival, sample not run	No
9904	Sample arrived at room temperature, sample not run	No
9905	Sample arrived thawed, sample not run	No
9906	Sample arrived frozen, sample not run	No
9907	Vial damaged, sample not run	No
9908	Vial leaked during shipment, sample not run	No
9909	Incorrect blood drawing tube, sample not run	No
9910	Low volume, sample not run	No
9911	Contaminated sample, sample not run	No
9912	Gross hemolysis, sample not run	No
9913	Moderate hemolysis, sample not run	No
9914	Excessive ANA - difficult to read, sample not run	No
9915	Vial unlabeled, sample not run	No
9916	Vial mislabeled, samples not run	No
9923	Vial contained only plasma, sample not run	No
9924	Aprotinin not added, sample not run	No
9925	Blood clotted, sample not run	No
9926	Bad Duplicates, sample not run	No
9927	Sample was unreadable, especially after running it	No
9928	Sample failed to be analyzed	No
9929	Vial number is associated with 2 or more subjects; clinical center unable to determine which subject vial belongs to	No
9930	Sample left at room temperature for a significant amount of time prior to processing	No
9931	Sample arrived without paperwork – subject that sample is associated with was not able to be identified	No
9932	Data questionable, do not use in analyses	No
9933	Low RQS and DV200<0.63, sample not run	No
9934	Low DV200 (<0.3), sample not run	No
9935	Low RNA concentration, sample not run	No
9936	Low DNA concentration, sample not run	No

*This list is subject to change.

19. TEDDY Physical Activity Assessment

NOTE: In August 2018, the collection protocol was changed so as to continue to collect physical activity assessments annually from subjects who are single or multiple persistent confirmed autoantibody positive (even if the subject reverts to autoantibody negativity) and to stop physical activity assessments on all other subjects after the 10 year visit. Should a subject be deemed single or multiple persistent confirmed autoantibody positive after the 10 year visit, the physical activity assessment will be restarted at the next visit. This will provide a complete dataset on all subjects up through 10 years of age and continued collection on persistent confirmed autoantibody positive subjects through the end of the study. Continued data collection on persistent confirmed autoantibody positive individuals will enable the TEDDY study to explore the role of energy expenditure changes through early adolescent years, on progression to T1D. These data will enable TEDDY to include physical activity patterns in assessments of T1D risk along with other exposures and changes occurring during the peri-pubertal period to include energy intake (diet), growth, hormonal changes and glucose demand. It has been recognized that glycaemia can be influenced by activity levels. As well, epidemiological data points to increased T1D incidence during this period, TEDDY has also observed a declining rate of conversion from autoantibody negative to autoantibody positive (i.e., lower incidence of seroconversion during this age range). This reduces the statistical power to see an effect of activity level changes during the 10-15 year age range. Coupled with a lower compliance rate, as compared to children willing to wear the actigraphs among children who are persistent confirmed autoantibody positive, it seems prudent to reduce the burden on children, families and clinic staff by discontinuing data collection after 10 years of age for families whose child is autoantibody negative. TEDDY will have a complete data set on this population through age 10 years so it will be able to address the contribution of activity levels in the cumulative incidence of islet cell autoimmunity up to this age.

19.1 Rationale

The Accelerator and Overload hypotheses have been put forward by Wilkin (2001) and Dahlquist et al (2006) as etiological models for type 1 diabetes (T1D). Wilkin's accelerator hypothesis postulates that both T1D and type 2 diabetes mellitus (T2D) have essentially the same etiology, namely beta cell insufficiency. The two diseases differ in the speed at which total beta cell loss occurs. Three component processes are thought to be involved: (1) constitution, characterized by a high rate of beta cell apoptosis (due to genetics or fetal priming); (2) insulin resistance due to overweight and rapid growth; and (3) autoimmunity found in genetically predisposed children that leads to rapid beta cell destruction and type 1 diabetes (T1D). The autoimmunity observed in T1D speeds up or accelerates the same underlying process that occurs at a slower rate in T2D. Childhood overweight increases insulin resistance and is thought to be a central causal factor in both.

The overload hypothesis developed by Dahlquist et al (2006) is very similar to the accelerator hypothesis but emphasizes a variety of factors linked to insulin resistance, such as overfeeding, puberty, inadequate physical activity, and beta cell overload or hyperfunction associated with psychological stress, inflammation, and cold climate. Dahlquist also argues these factors contribute to diabetes onset and disease progression even in those who have developed autoimmunity.

Both theories suggest that TEDDY investigators should monitor exercise and fitness in conjunction with other parameters associated with insulin resistance and beta cell overload such as body mass index, consumption of foods with a high glycemic index, total caloric intake at a given meal, psychological stress, and illness.

We will use accelerometers to objectively measure physical activity in the TEDDY study subjects and to test the following hypotheses:

- Low rates of physical activity, high body mass index, a pattern of high caloric intake in a single meal, and high consumption of foods with a high glycemic index are associated with the development of persistent anti-islet autoantibodies in genetically at-risk children.
- Low rates of physical activity, high body mass index, a pattern of high caloric intake in a single meal, and high consumption of foods with a high glycemic index are associated with more rapid progression to T1D in children who have developed persistent anti-islet autoantibodies.

TEDDY will use the Actigraph® model GT3X+ to assess physical activity because the Actigraph® accelerometer has been well validated in clinical and community-based physical activity studies involving children and adults (Trost et al 2005). It enables researchers to examine the duration of physical activity at varying levels of intensity and is capable of counting steps per day as another objective measure of physical activity. Data from both adults and children suggest negative association between daily sleeping hours, body weight and consumption of carbohydrates (Weiss et al. 2010). We will collect the sleep duration data in addition to the object accelerometer data and explore the relationship in TEDDY cohort.

References

Dahlquist G. Can we slow the rising incidence of childhood-onset autoimmune diabetes? The overload hypothesis. Diabetologia 2006;49: 20–24.

Weiss A, Xu F, Storfer0Isser A, Thomas A, Levers-Landis CE, Redline S. The association of sleep duration with adolescents' fat and carbohydrate consumption. Sleep 2010; 33(9): 1201-9.

Wilkin TJ. The accelerator hypotheses: Weight gain as the missing link between type I and type II diabetes. Diabetologia. 2001;44:914-922

Trost S et al. Conducting Accelerometer-Based Activity Assessments in Field-Based Research. Medicine & Science in Sports and Exercise. 2005;37 (11 Supple) S531-43

19.2 Training for Activity Assessment

19.2.1 General Training

All TEDDY staff members engaged in data collection must be trained and practiced in the cross-disciplinary elements common to the TEDDY protocol to be certified to engage in study activities. The cross-disciplinary elements of the training are the same for the life of the study and include:

- Successful completion of Humans Subjects Protections Training course.
- Successful completion of the centralized training or review of videos and presentations under the direction of a certified trainer.
- Reading the Manual of Operations and the TEDDY protocol related to all visits.
- Training and testing of coding accuracy to ensure cross-site comparability of coding.

Activity Field Personnel Groups

Field personnel are defined as study nurses and physicians (in Sweden and Finland), and clinic interviewers and sport scientist (in the US and Germany) who are responsible for collecting data in the field. All field personnel will learn how to instruct the participating families on activity assessment protocol during clinic visits. TEDDY long distance subjects will be informed through existing venues as specified in the TEDDY protocol.

A site lead activity person is defined as an individual responsible for overseeing the execution of the activity assessment protocol at each site and functions as liaison between the DCC and the sites who will participate in periodic conference calls to review the implementation of activity assessment protocol, make necessary changes, and inform interviewers of decisions that impact daily data collection. The lead activity persons for Finland, German, and Sweden are located in Turku, Munich, and Malmö, respectively. Each of the three US sites will have its own lead activity person. The lead activity person at the DCC will work with the lead activity persons at all sites and oversee the entire activity assessment protocol.

To achieve standardization and accuracy of the research interview, activity field personnel and site lead activity persons must fully understand the TEDDY protocol and their individual responsibilities for the study.

Interviewer Training

A central in-person training session was given on March 29, 2011 in Clearwater, FL, which covered accelerometry principles, technical orientation on using the ActiLife software and accelerometers, as well as instructions on administering the accelerometer and activity log. Extracting key information from returned logs and online data entry were also discussed. Other areas of importance included:

- Instruction to prepare and clean the accelerometers.
- Strategies to enhance subject compliance and timely return of the device.

- Emphasis on wearing the accelerometer for seven (7) consecutive days, including the time of sleeping.
- Emphasis on permitting only the TEDDY subjects to wear the accelerometer.
- Instruction to probe for specific durations of biking and water activities (e.g. swimming).
- How to check the quality of a returned activity log.

Video recording of this training is posted on the TEDDY website, media center so that study personnel can review at anytime. The site lead activity staff can also use these videos to train staff who were absent at the in-person training and/or need to be trained in languages other than English.

The activity assessment consult, Dr. Stewart Drost, also gave a background presentation at the TEDDY meeting in September, 2011. His presentation titled "Optimal Measurement Strategies for the Assessment of Physical Activity in Young Children" was also videotaped and is available for review on the TEDDY website media center.

19.2.2 Continuing Education

Lead activity personnel from all sites will schedule conference calls as needed to answer questions raised during data collection and coordinate continuing education efforts. They will also receive instructions on accelerometer updates and software upgrades from the DCC. It is recommended that the lead activity person at each site observe staff demonstrating the data collection process to the caretakers during clinic visits and give immediate feedback to the staff. All staff involved in collecting activity data should have at least one visit per year observed by lead activity personnel.

Clinic staff at all sites are encouraged to review the TEDDY Manual of Operations and/or the central training video throughout the project period in order to remain well versed in TEDDY specific protocol issues. The site lead activity person may hold refresher sessions periodically to address problematic areas and remind interviewers of the protocol. Such sessions can be either added to existing staff meetings or conducted separately.

Finland: Clinics can add the physical activity assessment topics to the established quarterly (four times a year) nutrition-related continuing education for study nurses.

Germany: All TEDDY staff in Munich participate at a meeting twice a month where topics of interest will be discussed.

Sweden: Group meetings are held with the lead activity staff and study nurses 3 – 4 times per year in the main clinic in Malmö.

US: The lead activity persons hold periodic (e.g. bi-weekly or monthly) meetings with interviewers at every site to communicate about strategies facilitating compliance and other topics related to physical activity assessment.

19.3 Data Collection Overview

TEDDY subjects aged 5 years and older will be asked to collect activity data once per year immediately after the TEDDY birthday visit (see Table 1).

> NOTE: In August 2018, the collection protocol was changed so as to continue to collect physical activity assessments annually from subjects who are single or

multiple persistent confirmed autoantibody positive (even if the subject reverts to autoantibody negativity) and to stop physical activity assessments on all other subjects after the 10 year visit. Should a subject be deemed single or multiple persistent confirmed autoantibody positive after the 10 year visit, the physical activity assessment will be restarted at the next visit.

The data collection week is expected to follow the birthday visit as closely as possible. The subjects and caretakers will receive verbal instructions on how to wear the Actigraph® accelerometer (referred to as the monitor or meter below) and how to complete the activity log (referred to as the log below) at the visit. The TEDDY staff will then schedule data collection with the family, hand out one fully-charged, initialized, and belted monitor, a blank activity log, and other instructional materials. A well-padded correctly-labeled pre-paid return envelope (or similar) will be provided to TEDDY families to return the monitor. Subjects will be reminded to wear the accelerometer in the middle of the data collection week and be reminded to return the monitor and the log in the mail as soon as the data collection is over. Upon receipt of monitor back at the TEDDY clinics, a staff will inspect monitor condition, download the data from the monitor to a local computer, upload the file to the DCC, and enter the activity log to an online consolidation form. Incentives such as pedometer can be used before or after data collection to promote or appreciate subject compliance. Returned logs are to be kept in every clinic following local research ethical review board policy (e.g. institutional review board in the U.S.)

Reminder phone calls and/or emails are to be made if the TEDDY clinics do not receive the monitor 7 days after data collection.

The subjects will not be asked to repeat data collection if less than 7 days of data is recorded on the accelerometer or if any equipment failure takes place during data collection.

If activity data cannot be collected soon after the birthday visit, study staff may allow the subject to complete data collection at any convenient week. If this alternative does not work for the family, the collection may be postponed to be after the mid-year visit (i.e. the visit between two consecutive birthdays). TEDDY allows 6 months prior to and 6 months after the birthday visit for the activity data collection, which means every subject has 12 months to complete this protocol at any age.

Table 1. **Activity Assessment Schedule**

	Clinic Visit (age in years)* **																			
	Follow-Up																			
Sampling Frequency	**5**	**5.5**	**6**	**6.5**	**7**	**7.5**	**8**	**8.5**	**9**	**9.5**	**10**	**10.5**	**11**	**11.5**	**12**	**12.5**	**13**	**13.5**	**14**	**14.5**	**15**
Physical Activity Assessment**	**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**

** A 6-month window is scheduled prior to and after every birthday visit for the physical activity assessment, which means a subject has 12 months at every age to complete this assessment.

*** NOTE: In August 2018, the collection protocol was changed so as to continue to collect physical activity assessments annually from subjects who are single or multiple persistent confirmed autoantibody positive (even if the subject reverts to autoantibody negativity) and to stop physical activity assessments on all other subjects after the 10 year visit. Should a subject be deemed single or multiple persistent confirmed autoantibody positive after the 10 year visit, the physical activity assessment will be restarted at the next visit.

19.3.1 Materials and Supplies

The following materials and supplies are needed to complete the activity assessment:

1) ActiLife software and ActiLife Manual
2) Actigraph® GT3X+ accelerometer
3) USB charging ports
4) Black elastic belt with buckle attached
5) Activity log – blank copy, instructions, and sample.
6) Meter Q&A handout–with local TEDDY contact information filled in
7) Meter Wearing Key Points handout - with local TEDDY contact information filled in
8) Letter for Teacher handout - with local TEDDY contact information filled in
9) Pre-paid pre-labeled return envelope or box with bubble padding included. Also include insulation sheet as needed.
10) Sample graph of the accelerometer data
11) Incentives (e.g. pedometers)

19.3.2 Activity Log

The activity log (Appendix 19A) is designed to collect complementary data due to the technical limit of the activity monitor. The caretaker or the subject (when capable) is asked to record the durations of sleeping, bathing, bicycling, downhill skiing, snowboarding, and water activities(e.g. swimming) and indicate if the activity level is typical in every day during data collection. Total duration of competitive and/or structured activities performed in a day is also to be noted *only if the activity monitor was taken off during such activities.* The activities to be considered are listed below. *There is no need to* indicate the duration of these activities if the child kept wearing the monitor during practice.

1. Physical Education Class (P.E.)
2. Track and Field
3. Any sport played with a ball (such as American football, touch football, soccer, basketball, baseball, softball, tennis, badminton, field hockey, ice hockey, table tennis, handball, floor ball, golf, polo, water polo, lacrosse, etc)
4. Cheerleading
5. Gymnastics
6. Wrestling
7. Fencing
8. Other snow sports except downhill skiing and snowboarding
9. Skating (including figure skating and short track)
10. Rollerblading
11. Dance
12. Martial Arts
13. Surfing

14. Rock Climbing (indoor or outdoor)
15. Horseback riding (including jockeying)

The subjects and caretakers will receive in-person explanation on completing the log during TEDDY visit as well as written instructions before data collection. Study staff need to point out that the *most important* fields to be completed are the date and time the meter was removed because they provide key information for data reduction and analysis.

After scheduling the data collection with the parent, TEDDY staff will need to clearly label data collection dates, Subject ID, Local ID, and Meter Serial Number on the log. It is IMPERATIVE that the scheduled dates and time are clearly marked on the blank log and in local tracking system (see section "Accelerometer Distribution, Inventory and Tracking") and the monitor is initialized to start collecting data from midnight (12:00 AM) of the 1st day before being given to the subject.

Clinic staff will review the returned log and enter it into the online "Activity Consolidation Form". No teleform option is available for the log. Detailed instructions can be found in Section 19.6.1 "Enter Activity Log Online".

19.3.3 Prepare the Accelerometers

The Actigraph® GT3X+ accelerometer, referred to as the monitor or meter below, is only ready for use when it is cleaned, belted, fully charged and correctly initialized. This section addresses the key points in preparing the GT3X+ monitor for initialization. Check for cracked case or other damage upon receiving the returned monitor in the mail. Notify the DCC of any aesthetic or functional damage (e.g. battery not working).

As of January 2014, the GT3X+ model was discontinued and was replaced by the wGT3X-BT device. This new device collects data in the same manner, with additional features as well (such as BlueTooth, etc). When asked if there is any difference in terms of how to use this new model (initialize and data download) and whether the subjects will notice any difference, the company stated "In terms of device differences in initializing, etc; No, there is not a difference in this process. Nor will the participants see/feel a difference in devices. These devices are very similar, and collect data in the same manner. The main difference is simply the BlueTooth LE technology, which will open up doors for this particular device's future capabilities." TEDDY does not plan on using the BlueTooth function. The site can choose whether or not to mention it to the subjects.

The "TEDDY Template" developed for the ActiLife software was revised so that the computer will recognize this new model. The latest template (TEDDY Template_Sept15) can be downloaded from the TEDDY website, Data Forms folder, Physical Activity Assessment (page 4). Please download this latest copy even if you do not currently use the new model because this template file affects both the old (GT3X+) and the new (wGT3X-BT) models.

Clean the Accelerometers

- Use isopropyl alcohol wipes or Clorox® wipes to clean the exterior of the monitor. Do not use bleach or other cleaning solvent.

- Do not immerse the monitor into any liquid because it is not water proof.
- NO NEED to unscrew the back of the monitor during cleaning.

Belt the Accelerometers

- Every monitor is supplied with one black elastic belt and one plastic side-releasing buckle. The study personnel will lace the belt through the side loops of the monitor and attach the buckle to both ends of the belt securely, as shown in the picture.

- It is OK that the belt covers the serial number at the back of the monitor. If the elastic belt is not long enough for the subject, a longer belt can be used or two belts could be connected to comfortably secure the monitor around the waist. The DCC will purchase additional belt material and send to the sites. A 36 inch (91.4 cm) long belt is budgeted for every subject. The sites may customize the belt length.
- A new belt is to be used when sending an accelerometer to a different subject.

Accelerometer Serial Number

Every accelerometer has a unique serial number that is printed on a sticker at the back of device. The sites should copy the serial number prior to the first use of every monitor and make a replacement sticker when the original sticker starts to wear off. Always maintain legible serial number on every unit as it is the ONLY identifier to match a monitor with a given subject.

Cover the Accelerometer USB Port

Special attention is needed to ensure the monitor USB port is securely covered by the plastic cap on the end of the black rubber flap.

- All monitors should come with the USB port covered. To reveal the USB port, twist the cap counter-clockwise using the provided plastic pick or the edge of a coin.

** Using a flat head screwdriver is discouraged because it will chew up the plastic.

- The "open/close" instructions printed on the cap may come off after multiple use, therefore it is important to remember "turning clockwise" to close/lock the cap and "turning counter-clockwise" to unlock the cap.

It is important to keep the cap fully locked at all times because this cap blocks water from wetting the inside of the monitor. However, this cap, even when locked, is VERY easy to pop open during data collection (e.g. inadvertently twist it open when changing clothes). Therefore, in addition to locking the cap before mailing the monitor, study staff needs to remind the subjects and parents to keep an eye on the cap and make sure it stays in.

The other end of the flap where it is connected to the monitor is also likely to break after multiple uses. It is critical that 1) study staff lock the cap before mailing the monitors, 2) study staff caution the subjects and parents not to play with it during data collection and put in back in place gently when necessary, and 3) clinic staff check to see if it is missing or broken after the monitors are returned. In the event of broken rubber flap, study staff will contact the DCC for repair.

Lost & Found Sticker

One "lost & found" sticker is recommended to be pasted on the front side of the monitor so that the TEDDY clinics can be notified if a monitor is accidentally dropped or lost. The sticker could also serve as reinforcement to the black rubber flap. The sticker should not exceed 2 cm x 2 cm size and should not cover the monitor serial number on the back of the monitor. An example of the sticker is shown below:

TEDDY MOO

TEDDY Study
If found,
please call
xxx-xxx-xxxx

Charge the Accelerometers

The charging process automatically starts when the monitors are connected to a power-on computer or a USB charging port. The ActiLife program is not needed to charge the device. The DCC will purchase and distribute USB charging ports to the sites.

The Actigraph® GT3X+ monitor has one red LED light and one green LED light which flash in various patterns to indicate battery level (see Table 2 below, cited from the ActiLife Manual)

Table 2. GT3X+ Accelerometer LED Lights Reference Table.

Actigraph® GT3X+ Connected to PC	
Red LED (Fault Indicator)	
2 Flashes	Li-Ion Battery is Faulty
3 Flashes	A hardware failure occurred while recording data. Contact the DCC.
Green LED	
1 Flash	Battery charging
Multiple Flashes	Communicating with PC via USB
Steady On	Battery fully charged
Actigraph® GT3X+ Not Connected to PC	
Red LED (Fault Indicator)	
No Flashing (LED Off)	Normal operating condition (e.g. monitor fully charged but not initialized)
2 Flashes	Low Battery (use ActiLife software to check for remaining battery life). The unit needs to be recharged.
3 Flashes	Unexpected battery failure (temporary battery power loss) Or Battery Level has fallen below 3.1V and the unit has entered Halt Mode
Green LED	
No Flashing (LED Off)	Actively collecting data (“Flash Mode” disabled) or battery dead
1 Flash	- Delay before start mode (the LED always flashes prior to starting data collection) - Actively taking data ("Flash Mode" enabled – not recommended)

2 Flashes	N/A
3 Flashes	- End of memory reached (Device no longer collecting data) - Battery died while unit was in delay before start mode (no data collected on device)
Note: The Red LED will ALWAYS flash to indicate LOW BATTERY regardless of whether "Flash Mode" is enabled or disabled. If a "stop time" (not used in TEDDY) has been reached, the Green LED will stop flashing all together regardless of its previous state.	

Always charge the monitor before sending to the subject. Charging time will depend on the battery level, but typically will not exceed four (4) hours for a fully depleted battery (3.1 volt or lower). Once the battery is fully charged, the red light will remain illuminated as long as the monitor stays connected to the computer or the USB charging port. The maximal battery power is approximately 4.2 ~4.3V.

Note: the ActiLife software will not initialize the monitor if the voltage is below 3.85 volts. If any monitor has a voltage less than 4.1 volts, we recommend leaving it connected, allowing it to charge fully before initialization.

When the battery discharges to 3.1 V during data collection, the device will enter a "HALT mode" to stop data collection before the battery power drops further. In the meantime, the red light flashes three times. In this mode, all important variables are stored in the monitor so as to secure the device download. The accelerometer **cannot** be recharged and redeployed in HALT mode, and must be downloaded and reinitialized to continue use.

To maximally preserve the capacity of the lithium ion battery, it is recommended that monitors be stored in a fully charged state in low ambient temperatures. Devices remaining in storage should be recharged to this level every two to three months. Table 3 below (cited from the ActiLife Manual) demonstrates the impact of storage temperature and charge state on the long term capacity of the batteries.

Table 3. Lithium Ion Battery Capacity

Temperature	Remaining capacity at 40% charge (recommended storage charge level)	Remaining capacity at 100% charge (typical user charge level)
0^0C (32^0F)	98% after 1 year	94% after 1 year
25^0C (77^0F)	96% after 1 year	80% after 1 year
40^0C (104^0F)	85% after 1 year	65% after 1 year
60^0C (140^0F)	75% after 1 year	60% after 3months

19.3.4 Operation of the ActiLife Program

The ActiLife software is designed in Lite and Full editions. Every TEDDY clinic has two copies of the Lite edition to operate the accelerometer. The DCC will install the Full version which has additional data process functions.

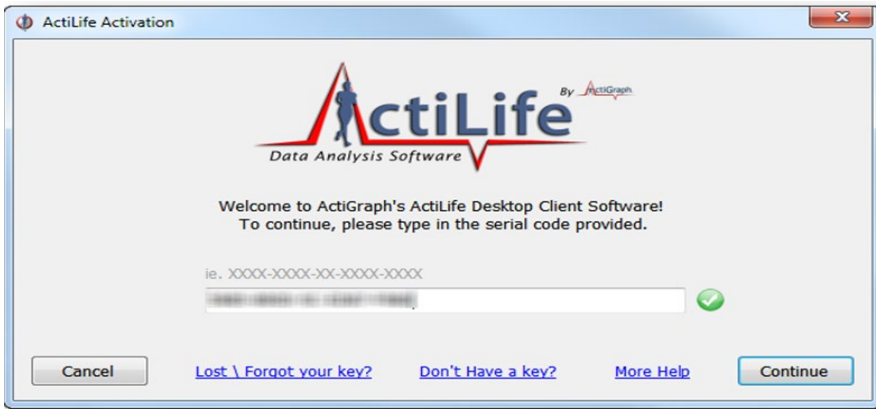
The DCC keeps the software licenses and support agreement documents and forwards the sites the ActiLife Manual and contact information for technical support and troubleshooting assistance from the DCC and/or the manufacturer. License agreements do not permit copies of the software to be made. Local Clinical Center sites are responsible for software security and local backup, redundancy and disaster recovery procedures for their copies of the software.

Detailed instructions regarding this software are available in the ActiLife Manual published by the Actigraph® company. You can access the latest version (v13.3.3as of Aug 3, 2016) and future revisions online at www.theactigraph.com/actilife. Given that the ActiLife Manual covers both the Lite and Full editions, key information applicable to the Lite edition is presented in this MOO.

Install ActiLife Software

Install the ActiLife Lite Edition under the Windows operating system. This software IS NOT COMPATIBLE with Macintosh systems.

Follow instructions in the ActiLife Manual to install and activate the software. Internet connection and administrator rights are **required** to install the software. Navigate to http://www.theactigraph.com/actilife and click "Download". Double click on the downloaded file and follow the instructions. When prompted, type in the activation code provided by the DCC to activate the program (as shown below). Obtain assistance from your IT department if needed.



A shortcut icon "ActiLife" will appear on your computer desktop after successful installation.

**Only one usage of the activation code is allowed for every computer. Each site can use the activation code up to two times, meaning the software can run on two computers. If you want to run the program on a different computer, you need to first inactivate the program before installing and activating it on the destination computer.

**An ActiLife Introduction Tour is launched the first time you use the program. It is recommended that you take advantage of this function.

ActiLife Updates

The program automatically checks for firmware update and version upgrade every time you use it. Do not interrupt this process because this process is critical to ensure software consistency across all TEDDY clinics.

** The TEDDY license for the ActiLife software has been upgraded to version 6.8.0 or higher. as of February 2012 and is valid through August 26, 2020.

The DCC will notify the clinics when a revised ActiLife Manual is released and highlight major updates and/or changes. Updates and/or changes that are relevant to TEDDY will be noted in the MOO as well.

Customize ActiLife

Customize important settings of the ActiLife before initializing any monitor to ensure consistent data format across all TEDDY sites. When uploading the data file to the DCC, the system will automatically check for the required format. Data files that do not meet the requirement will not be accepted.

The DCC will provide a template which locks the following settings for the GT3X+ meters:

1. Checked "Enable Template for GT3X+"
2. Sample rate = 30 Hz
3. Unchecked "Flash LED in delay mode" and "Flash LED during data Collection" (the LED does not flash ebefore or during data collection)
4. Force naming convention = <Subject Name> <Start Date> ("Subject Name" = TEDDY ID_Local ID, see details in section "Initialize the Accelerometers")
5. Disable "Idle Sleep Mode"

All sites will load this template into their local ActiLife Lite edition to ensure consistent program operation across the study and to save work and time of the customization process. Given the manufacturer will likely to continuously modify the functionality of the template, the DCC expects to send revised templates accordingly during the course of TEDDY. This template file will be named as "TEDDY Template_(date).agt" and be emailed to the sites as well as be posted on the TEDDY website (about 4 KB size) every time a revision takes place. Updating the template will not affect other settings of your program.

To customize:

1. The first step is to load the template file. Download "TEDDY Template_(date).agt" from either your email or the TEDDY website, Data Forms section, Physical Activity Assessment folder. Save it to your local hard drive.

   *** If downloading from the TEDDY website, please remember to unzip it before the next step.*

2. Double click the .agt file to load the template to your ActiLife Lite.

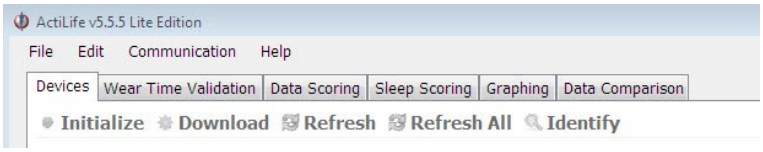
TEDDY MOO

3. After successful loading, you will see "Template:TEDDY" and the last modified date and time at the upper-right corner of the ActiLife window. This template can't be edited in the ActiLife Lite.

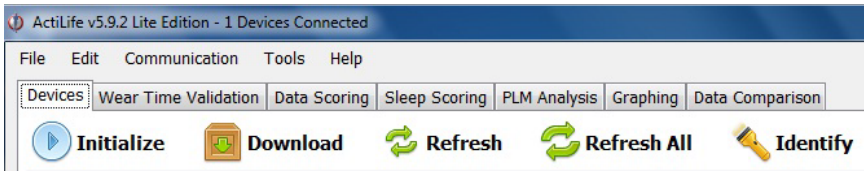
   ** The latest modified date is September 1, 2015.

Since the old model GT3X+ was discontinued as of January, 2014, the "TEDDY Template" was revised so that the computer will recognize the new model wGT3X-BT. The latest template (TEDDY Template_Sept15) can be downloaded from the TEDDY website, Data Forms folder, Physical Activity Assessment (page 4). Please download this latest copy even if you do not currently use the new model because this template file affects both the old (GT3X+) and the new (wGT3X-BT) models.

4. Now look at the top section of the ActiLife Lite window. "ActiLife Lite Edition" should appear at the upper left corner of the screen. Above the bolded "Initialize", there are six (6) tabs named Devices, Wear Time Validation, Data Scoring, Sleep Scoring, Graphing and Data Comparison.



   - This section will look slightly differently from November 18, 2011 (shown below) in that a different icon was used in newer version (v5.9.2 or higher) for each of the action buttons (i.e. "Initialize", "Download", "Refresh", "Refresh All" and "Identify") and a new tab "PLM Analysis" was added. The different icons are cosmetic changes only and the "PLM Analysis" function is irrelevant to TEDDY. The procedures to use this software remain the same.



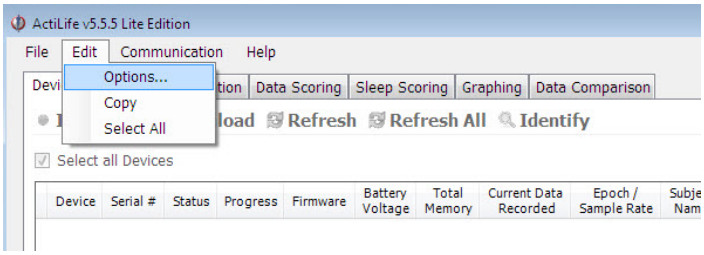
   - TEDDY will use only the Devices tab for data collection and download.

     *** The other tabs (including PLM Analysis) should be inactive in the Lite Edition.*

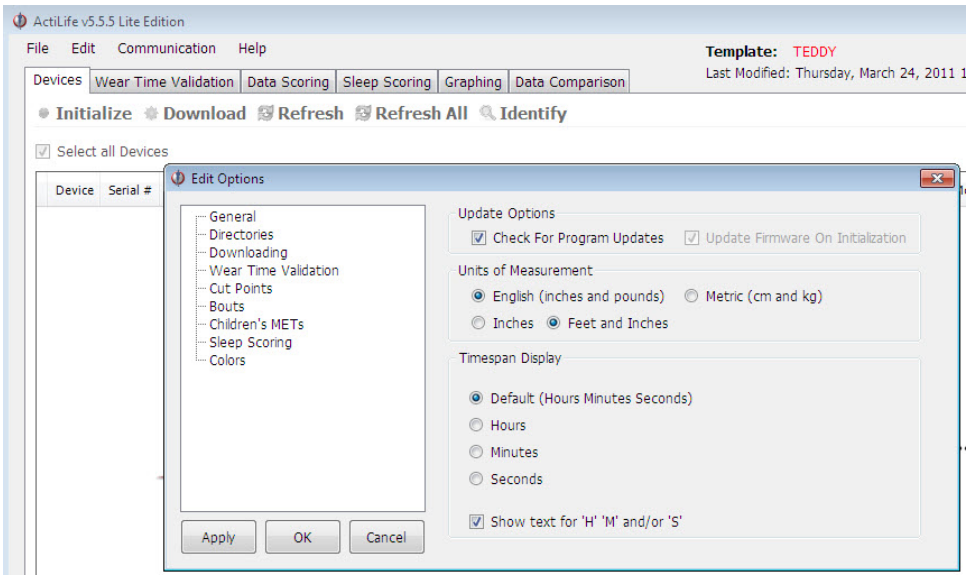
   - The inactive tabs have a message suggesting you to upgrade to ActiLife Pro. Ignore the message because TEDDY does not use the Pro edition (i.e. do not click on the message).

5. For the following customization process, make sure to click "Apply" at the end of every step to permanently save your settings.

6. Single-click the "Edit" menu at the upper-left corner of the ActiLife window and then single-click "Options…".

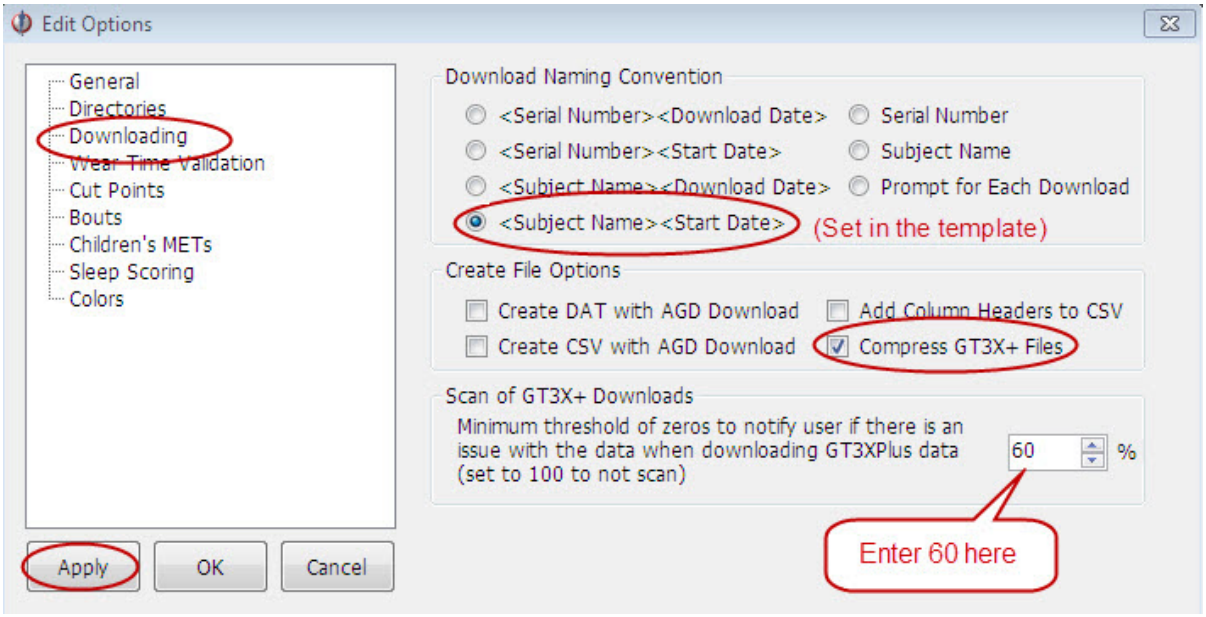


7. In the "Edit Options" window, <u>ignore</u> the top two topics "General" and "Directories". <u>Do not change any setting</u>.

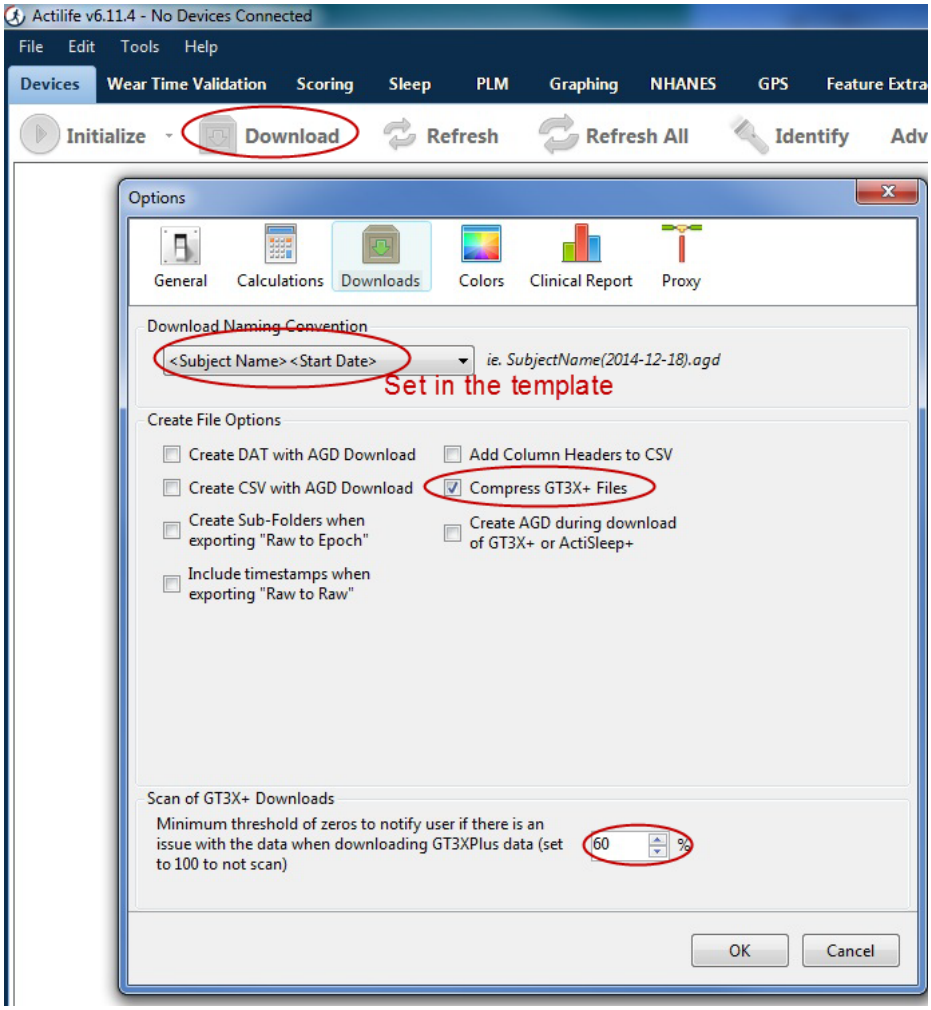


8. Click the next topic "Downloading". Check "Compress GT3X+ Files" under "Create File Options". A message "This will double the post-processing time" will appear. Click "OK" to close the message. Enter "60" under the "Scan of GT3X+ Downloads". Then click Apply.

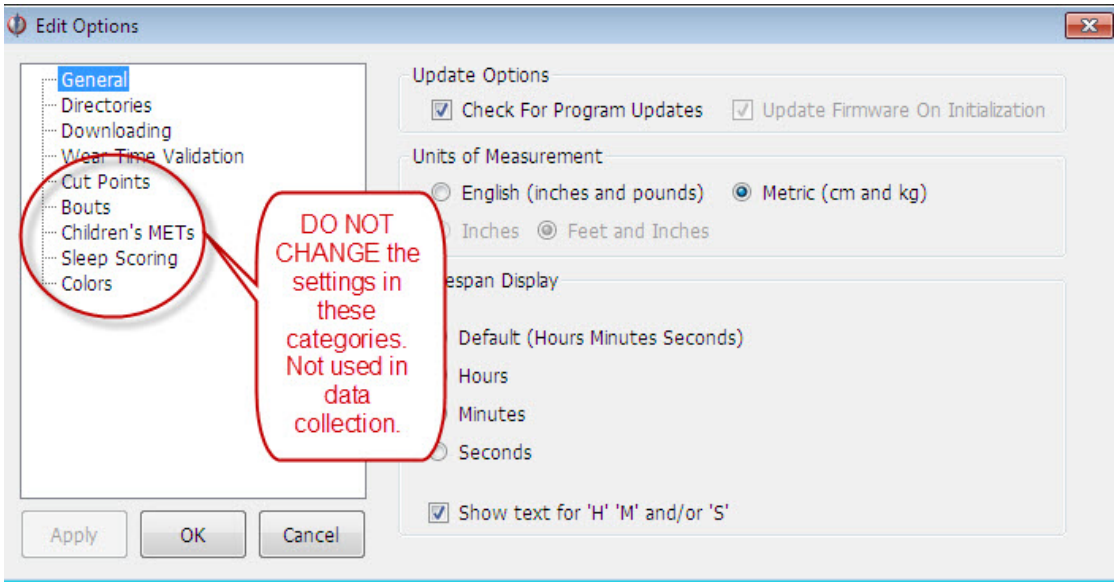
   **Ignore "Download Naming Convention" because the template already locks it to "<Subject Name><Start Date>", despite it may not be visible here.



In newer versions of the Actilife, the window looks like this:



9. There is no need to make changes in Wear Time Validation, Cut Points, Bouts or Children's METs, Sleeping Scoring and Colors because those topics do not apply to data collection.



10. Click OK to exit the window. You have now customized the ActiLife program according to TEDDY requirements.

Initialize the Accelerometers

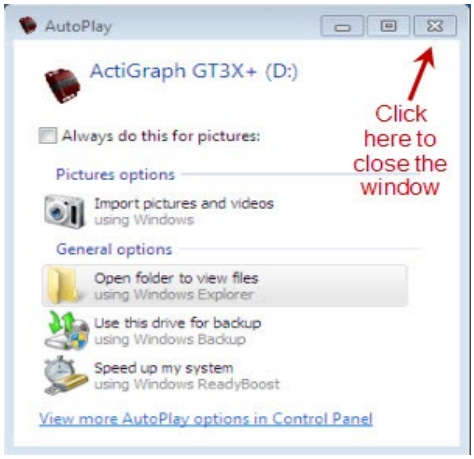
The activity monitors must be initialized before use. Initialization may be done any time after data collection is scheduled. It is recommended to initialize within 24 hours of sending it to the subject in order to maximally preserve the battery power for data collection.

IMPORTANT: Verify that the date and time is correct on all computers being used for initialization and data download. Do not change the time on the computers once the data collection begins. The monitor's internal clock will automatically synchronize with local time on the computer during initialization and update for summer/winter time change. Such time change will be handled at the DCC in data analysis.

Always make sure to download data previously recorded on the monitor before initialize for the next subject.

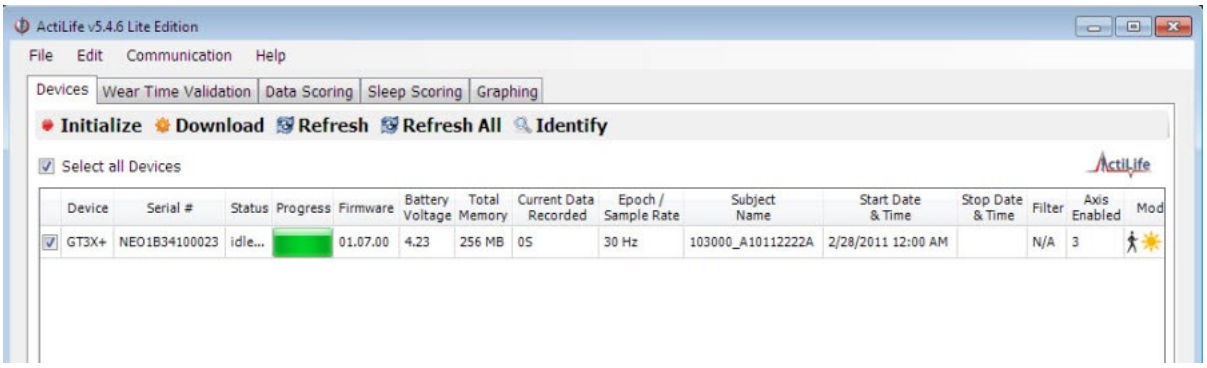
To initialize a monitor:

1. Connect the monitor to a computer using the provided USB cable before or after starting the ActiLife program. Pay attention that the smaller end of the USB cable has a contoured rectangle shape (one side is curved and the other side is straight). This design is to prevent incorrect insertion when connected to the monitor. Also note a black arrow is engraved on the smaller end. Make sure the black arrow faces down when connecting this end to the monitor.
2. Your computer will recognize the GT3X+ monitor as a portable memory device. An AutoPlay window (shown below) will likely to appear on your computer desktop. When you see this, click the upper right corn to close it or ignore it.

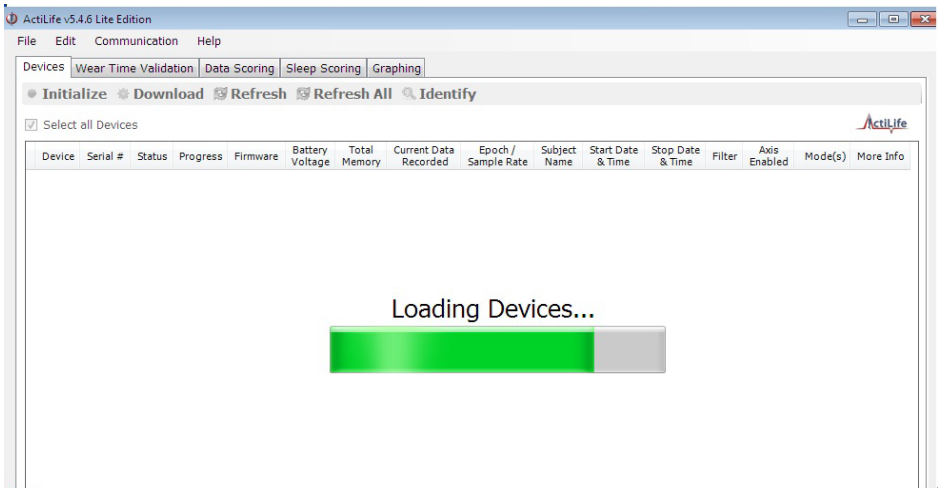


** When using desktop computers, it is recommend to connect the monitor directly to the rear USB ports instead of the ports on the side of the computer monitor. The rear ports are directly hard-soldered to the motherboard, and therefore it is not likely to lose current over a span of internal connecting cable. For laptops, there is no preferred port as there are all directly connected.

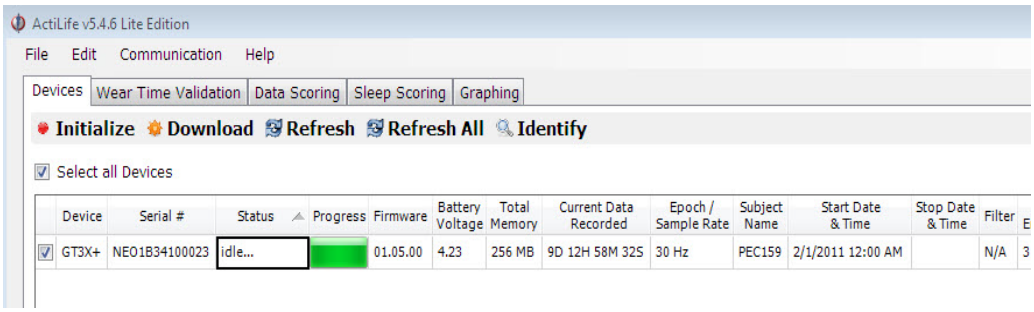
3. Double click the "ActiLife" icon on the desktop to start the program if you have not done so. Key parameters of every monitor will appear in the window as shown below. If accelerometers were already connected to the computer when starting the ActiLife, you will immediately see this window.



Note: If you start the program before connecting the monitor(s) to the computer, you will see messages such as "Please, plug in a device…" and "Loading Device…".



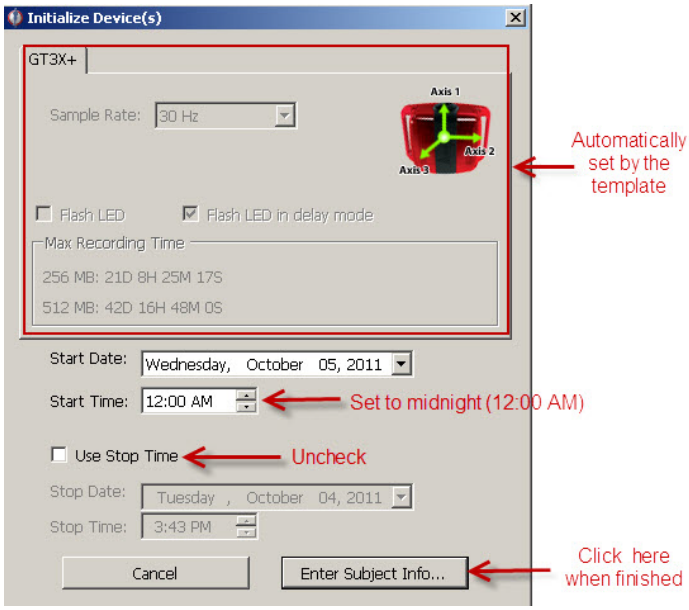
4. Select one or multiple monitors to be initialized. Then single click the "Initialize" button.



****The ActiLife software will not initialize the monitor if the voltage is below 3.85 volts.** If any monitor has a voltage less than 4.1 volts, please charge it fully before initialization.

** Use "Refresh" or "Refresh All" button to check for battery level if the monitor(s) have been charged for a while.

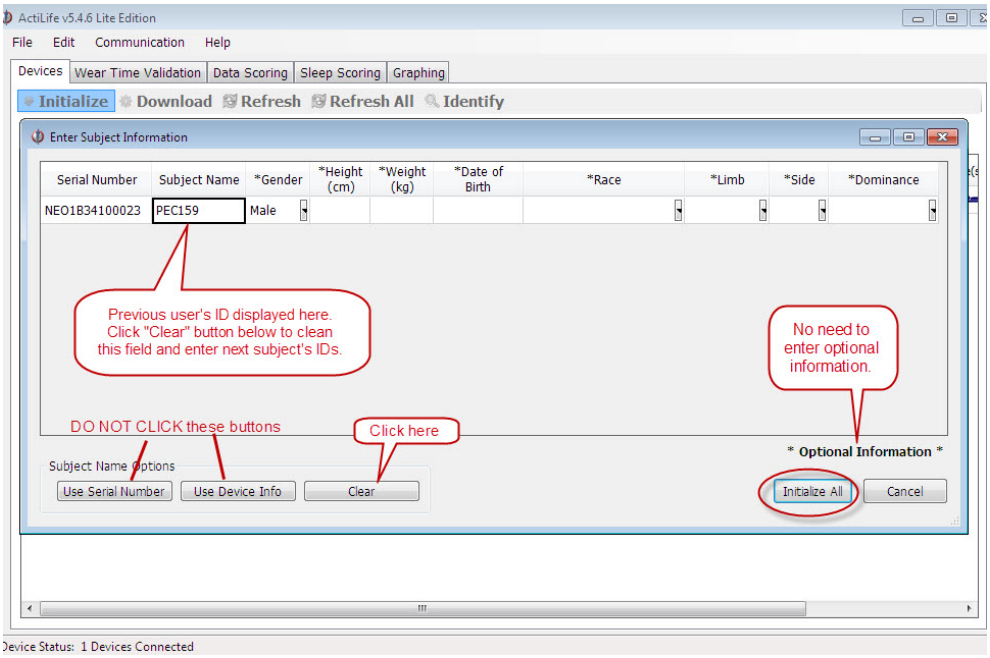
5. In the "Initialize Device(s)" window, follow the settings shown below to set the parameters. The template has locked the "Sample Rate" despite it may not be visible here. Use the pull-down menu to change "Start Date" and always set the Start Time at midnight (12:00 AM). It is optional to define a stop time. If you choose to do so, one suggestion is to set the Stop Date to be 21 calendar days after the Start Date and Stop Time at midnight (12:00AM). For instance, set the Stope Date to October 26 if the Start Date is October 5. Click "Enter Subject Info…" to continue.



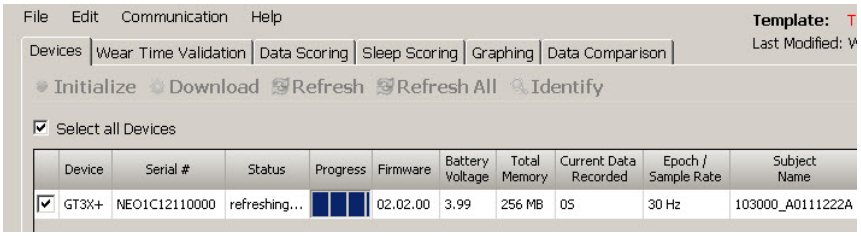
6. In the "Enter Subject Information" window, the monitor serial number(s) are pre-populated as well as the Subject Name(s) of previous user(s). Single click on the previously enetered subject name(s) and the press "Clear" at the bottom to empty the field. The empty cells should be highlighted in blue. Then single click the blue cells one at a time and enter the next subject's IDs.

   The correct naming schema is "Subject ID_Local ID". Any alphabet in the ID should be capitalized, for example, 103000_A0111222A (a Finnish subject). No need to fill in the fields marked with an asterisk * because they are not needed here and TEDDY has collected the information in other forms/questionnaires.

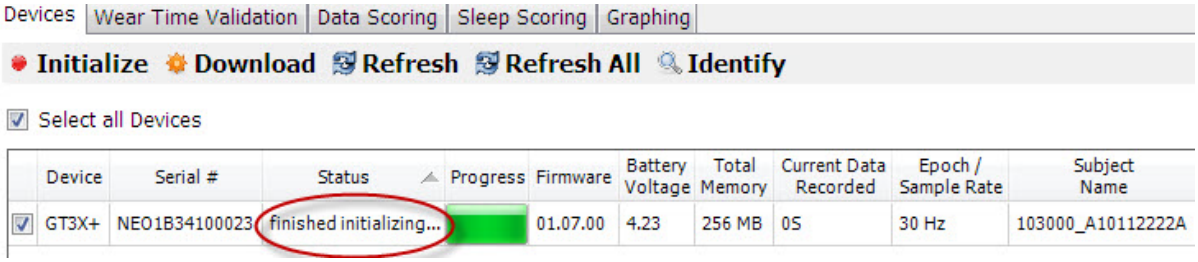
7. Click "Initialize All" after entering all subject names.



8. You will then see messages in the "Status" column showing the initialization process. Messages include "updating", "initializing", "refreshing", and "finished initializing…".



9. The message will be "finished initializing…" after the process is completed.



10. Before you disconnect the device(s) from the computer and send them out to subjects, make sure the monitor(s) are fully charged. A steady red LED light stays on indicating the battery is fully charged. A blinking light indicates it is still charging. Monitors to be charged can stay connected to the computer or be plugged into the USB charging port.

    ** When disconnecting the monitor from the computer, simply unplug it from the USB cable. It is not necessary to close the ActiLife software before disconnection or

use the Windows "Safely Remove Hardware" icon that commonly appears in your taskbar (the lower right corner of your computer screen).

11. Initialized accelerometer(s), when not connected to the computer or USB charging port, should have the green light flashing indicating the unit is ready for data collection.
12. Refer to the ActiLife Manual for more information on how to charge the battery.

    NOTES:

    ** Initialized monitors can stay plugged in to the computer to complete charging process.

    ** Multiple monitors can be connected to one computer and be initialized at the same time.

    ** In the event that you have any equipment failure (computer, software or the monitor), inform the DCC immediately.

    ** For the long-distance subjects, if a monitor has been initialized but not yet mailed out to and the data collection dates are changed, the monitor needs to be re-initialized to reflect the new starting day. If date change occurs AFTER the monitor has been mailed out but HAS NOT reached the recipient, the site needd to tell the caretakers to record the actual wearing dates on the log. In the case that the monitor is being shipped and the rescheduled dates are more than 7 days later than the original, the sites need to instruct the caretaker to mail back the monitor and re-issue another correctly initialized fully-charged monitor to the subject to ensure adequate battery power for data collection. Such incidents need to be thoroughly documented in the local tracking system.

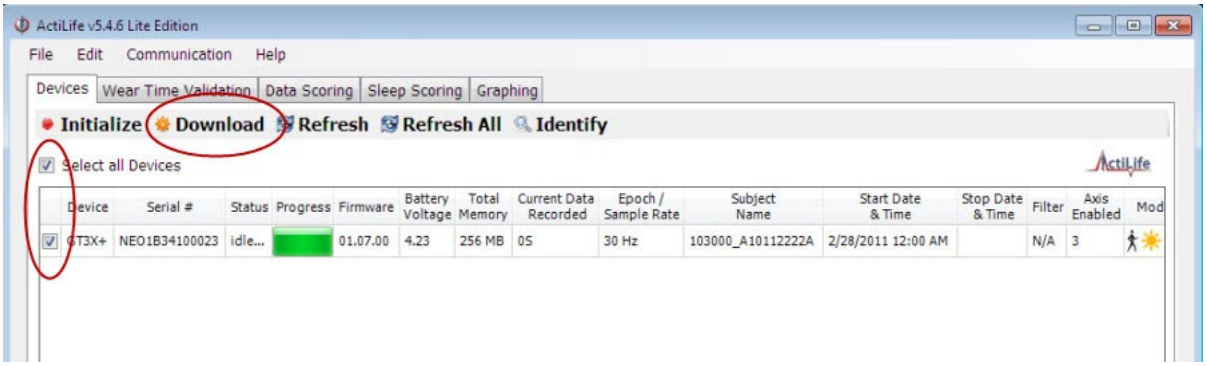
Download Accelerometer Data

Download monitor activity data as soon as the monitor is returned to the clinic (preferably within 48 hours). Refer to the ActiLife Manual for more details.

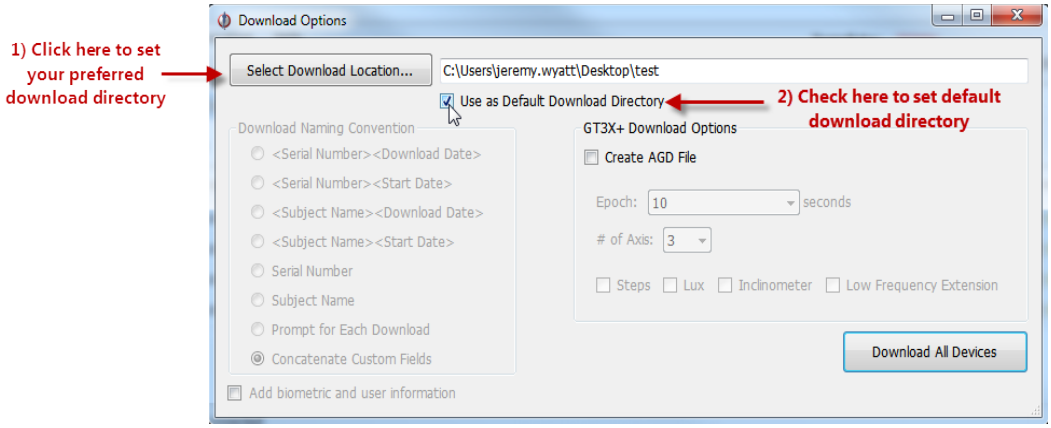
ALWAYS download data from an accelerometer before initializing it for the next subject.

To download data:

1. Start the ActiLife program before or after you connect the monitor(s) to the computer. You can plug in one or multiple monitor(s) at the same time.
2. Select the monitor(s) from which you want to download data. Then click "Download". Note that the "Current Data Recorded" field will not be zero.

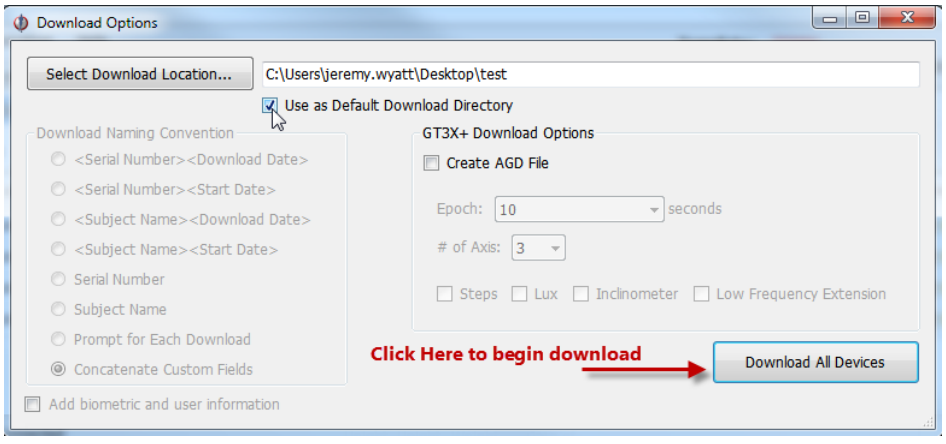


3. If this is the 1st time you download data, click "Select Download Location…" to designate a preferred folder to store the accelerometer data and check "Use as Default Download Directory" to save this setting. Uncheck the option "Add biometric and user information" because the DCC already has such information. Also uncheck "Create AGD File". Then, click "Download All Devices" to proceed.



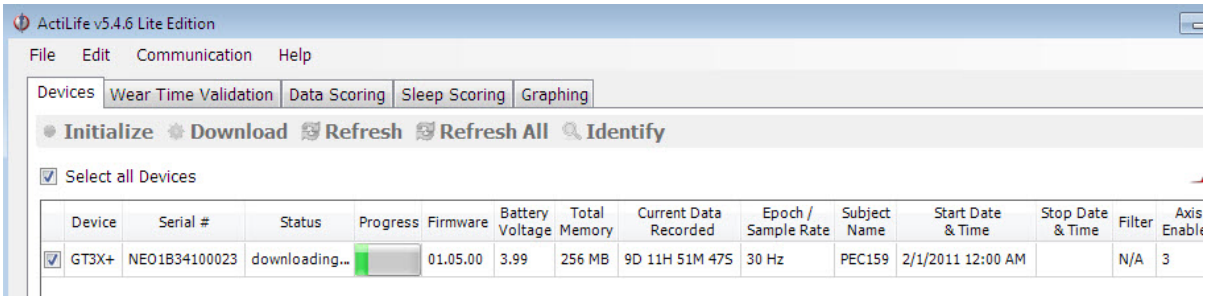
(Actigraph® Image)

** If you have designated the default download directory in previous use, you can simply click "Download All Devices" after making sure "Create AGD File" is not checked.

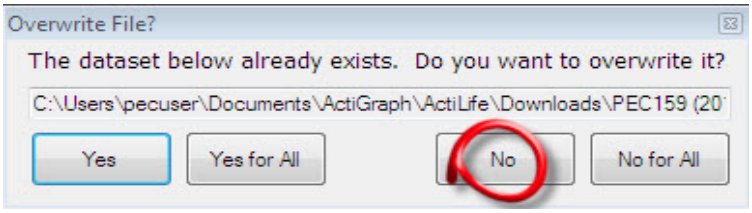


(Actigraph® Image)

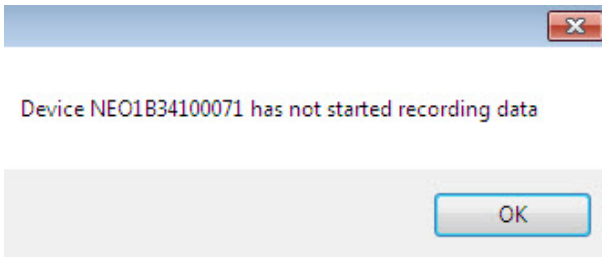
4. A “downloading…” message will appear under “Status”.



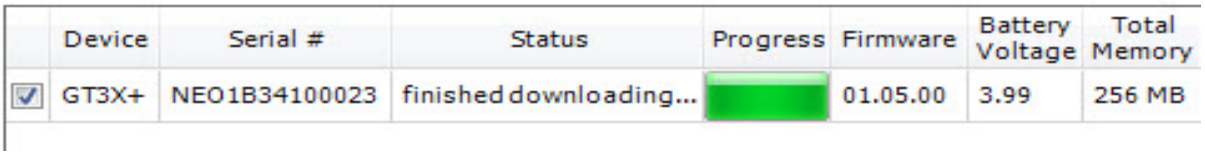
5. If the data you are downloading already exists in the destination folder, you will be asked whether or not to overwrite the file. Click “No” to exit the window.



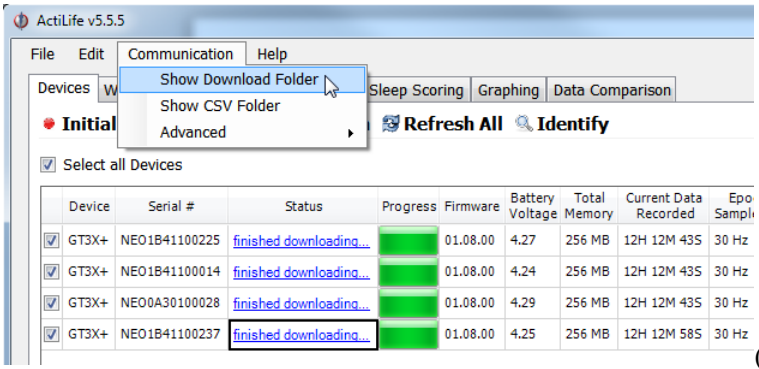
6. If a monitor was initialized and data collection has not started yet, the following notice will appear when you try to download data from it. Click OK to close the window.



7. A “finished downloading…” message will appear after data from all accelerometers are downloaded to your destination folder.

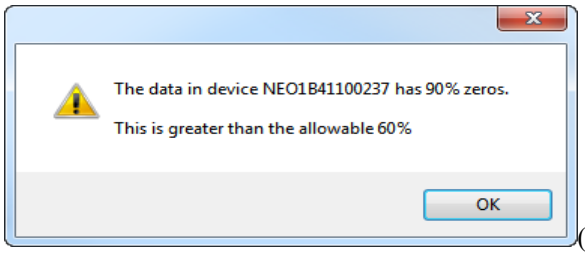


8. Click the “Communication” menu on top of the window and click “Show Download Folder”. This will open your default download folder which stores the data you have just downloaded.



(Actigraph® Image)

9. Below is a possible message that will appear after data download. This message indicates there is likely to be a problem with the device or subject compliance because we have set the "60%" threshold for "Scan of GT3X+ Downloads" (under Edit Options). When you see such message, first check the activity log to see if any reason was recorded to explain the missing data. If the activity log doesn't provide reasonable explanation, you will need to notify the DCC. A notice of "100% zeros" indicates that no data was collected.



(Actigraph® Image)

10. Upload the compressed .gt3x file(s) to the DCC (see section "Upload Accelerometer File").

    Note: Refer to "Frequently Asked Questions" section for troubleshooting.

19.3.5 How to Wear the Accelerometer

The monitor should be securely affixed around the waist and be as close to the center of the body as possible with the ideal location being the right hip. It can be worn either next to the skin or above light/thin clothing. However, the device **must be held snugly against the body** to prevent erroneous readings. The black rubber flap covering the USB port should be facing away from the body and remain vertical when the monitor is worn (see picture below).

19.3.6 Data Collection Package Checklist

This package should be assembled prior to the demonstration of the activity assessment protocol. The package should contain the following items:

1. One (1) fully-charged monitor with belt and buckle attached – to be initialized after scheduling with the family
2. One (1) copy of the blank Activity Log (Appendix 19A shows the new shortened log)
3. One (1) copy of the Meter Key Instructions – Optional. Fill in local TEDDY contact information (Appendix 19B shows the new version)
4. One (1) copy of the Meter Q&A – Optional. Fill in local TEDDY contact information (Appendix 19C shows the new version)
5. One (1) copy of the Letter for Teacher - Optional. Fill in local TEDDY contact information (Appendix 19D)
6. One (1) pre-paid pre-labeled return envelope or box with padding. If needed, also include insulation sheet and a rubber band (to secure the insulation sheet).
7. Sample Graph of Activity Data (optional handout to the subject) (Appendix 19E)
8. One (1) copy of the blank Activity Log supplemental page, Optional (Appedix 19 F shows the new version)

Appendices 19A, B, C, D, E, and F are posted on the TEDDY website under Data Forms section, Physical Activity Assessment folder. In the U.S., the DCC will work with a printing service to color-print the English and Spanish versions of Activity Log on cardstock and Key Instructions on regular paper and ship the hardcopies to the sites. Every U.S. clinic will print the black-and-white Meter Q&A, Letter for Teacher handouts, and the supplemental log on their own. The European sites are advised to arrange local printing and receive reimbursement from the DCC.

The Sample Graph of Activity Data is provided to enhance the subject's interest in wearing the acclerometer. The sites may laminate it or store it in page protector for repeated use during protocol demonstration. Alternatively, the sites may give a copy to the family.

19.3.7 Protocol Demonstration (Script)

Clinic staff will demonstrate the process of activity data collection to the subjects and caretakers during the clinic visit. Assemble a data collection package prior to the demonstration (see Section 19.3.6 above) and schedule monitor wearing dates after the demonostration.

A standard script is provided to introduce the data collection consistently among interviewers. Follow the script provided below and refer to separate instructional handouts as needed (Appendices B, C, D, and E).

> *[Use the word "meter" or "monitor", whichever is easier to understand, rather than "accelerometer". Remember to point out to the parents that a letter is provided to explain this part of the study to classroom teachers and that the parents can decide whether or not to use it.]*

TEDDY MOO

"Now I'd like to introduce you to a new activity in TEDDY – the activity assessment. We want to measure the regular activity level in subjects who are 5 years and older. What your child needs to do is to wear an activity meter around the waist for a week and in the meantime, we will need your help to record a few important numbers for us on a log sheet. I hope you will feel that it is a very simple task after I explain the process. Families who have tested out the monitor and log have told us that it is very easy and does not require a lot of effort on their part."

[If the parent is concerned about possible travelling during activity assessment, explain that it is fine to wear the monitor when travelling. Also assure the parent that security procedures associated with air travel or express mail (i.e., x-ray screening) do not adversely affect the monitor.].

[Show the parent the monitor and demonstrate how to fasten it around the waist]

"This monitor works in a way similar to the pedometer, but it captures movements in all 3 dimensions and gives more accurate measurement than the pedometers. It's the preferred instrument to use in research. "

[Give the monitor to the parent so that he/she can take a look.]

"As you can feel, it is very light and does not give any light or sound when collecting data. There are no buttons to push, so your child shouldn't be tempted to fiddle with it. The study plan is to ask [child's name] to wear this around his/her waist for 7 days in a row including sleeping time and school days. Do not give the monitor to other children or adults or pets in your household. We only want to measure [child's name]'s activity. When you are done, take it off and place it at a place with minimal disturbance because you don't want this monitor to capture other people's activities or your pets' movement or get damaged by accident."

[Make sure to emphasize 'sleeping time'. If the parent asks why it is important to sleep with the monitor, the reason is that sleeping hours may play a role in children's growth.]

"We have tested this meter in children of the same age. The meter didn't usually bother their sleep. And we have drafted a letter explaining why your child will be wearing a monitor at school. You can show it to the teacher if needed. Please emphasize to the teacher that only [child's name] can wear the meter and the meter should stay on him/her all the time. Before your child wears the monitor to school, it might also be a good idea to explain to your child that wearing the monitor is a very special and important thing for your child to do, and that it is only for your child. They should not allow their friends to play with it and they should not take it off."

[Show the letter to the parent and give a few minutes to read it.]

"Any questions?"

[Continue after answering the questions]

[Bring out the sample activity graph. It is recommended to show this graph to enhance the participant's interest. It is optional to give it to the family.]

"Here is a sample graph showing you the kind of data captured by this meter. These bars show the number of activity counts every 2 minutes between 4:30 and 6 in the afternoon. You can see very little body movement during things like snacking. The

higher counts suggest some structured activity or team sports. Again, low level of physical activity was probably due to homework, much more active during recess time, and low counts could be from movie watching."

[If asked, explain to the caretakers that the data will not tell us which specific activity the child did. We will analyze the intensity of the body movement.]

"You can now help your child wrap the monitor around the waist, on top of the right hip, and adjust the belt to comfortably secure it. It should sit snugly and not loosely. It can be worn next to the skin or above thin, light clothes, like a t-shirt."

"This monitor is not water proof and must be taken off during shower, bath, swimming or other occasions when the monitor may get wet. So please remember to take it off before any water activity. If your child takes swimming class at school or uses shower at school after sport practice, please tell him/her to take off the meter and put it back on as soon as possible. Playing in a water park is another example when you need to take off the meter."

[Pause for questions. If none, continue]

[Show the activity log with examples to the parent.]

"Given that this monitor can't be used for water activities, we will need you or your child to tell us how many minutes he/she swims when not using the meter.]

[Point to every field on the log as you go along.]

"Here are some examples. Write down total minutes of swimming and any other water activities for each day. If no swimming, just write zero. Other numbers we ask you to write down are the wake-up time and bedtime. We ask that [child's name] wear the monitor at all times except for water activities. If he/she participates in sport activities and NOT wearing the monitor for any reason, please tell us how long that lasted. No need to tell us every name of such sport, just tell us the total minutes in a day. Examples of the sport activities are listed in this Q&A sheet."

[Show the Meter Q&A and point out where the list of competitive/structured sports is printed.]

"To summarize, you just simply respond to all questions by writing down the minutes in the box. At the end of each day, indicate if the child wore the meter during sleep."

"We do not ask [child's name] to wear the monitor for extra make-up days if he/she forgets to wear it during the scheduled 7 days. But, if [child's name] wants to make-up for the missed days, please make sure to record the extra make-up days on the supplemental log."

"Do not forget to write down the final meter removal time on the original log."

[Pause and give time for the parent to read the log. Answer questions.]

"That's all you need to do for this new part of TEDDY. Just wear the monitor around the waist for a week and fill in the blanks on this log."

[Pause for questions. If none, continue.]

"We would like to schedule this data collection after today, as soon as possible. Your child will start wearing this monitor from the first day in the morning after waking up, keep it on for 7 days, and take if off 7 days later after getting up. Since the monitor has no on/off switch, we will program it in the lab so that it starts collecting data at the right time. This monitor will not make sound or give light when collecting data. It does not send wireless signals or waves. It will not injure your child during activities, even vigorous activities. And it will not affect [child's name]'s friends during team sports."

[Point to the Meter Q&A handout where it explains the meter light patterns]

"This monitor has two lights, one red, one green. They flash at different patterns to show battery level. It is explained in this sheet and we will send you a copy of this sheet."

[Show the Q&A sheets and Key Points handout to the parents. Allow the parents to read it, or you could go over it together with the parent.]

"We will give you a pre-paid pre-labeled envelope to return this monitor and the log after 7 days. Please put the monitor in this bubble pouch and seal it well before putting it in this envelope. That'll give enough protection during shipping."

[If needed, European study staff also need to explain how to use the insulation sheet to protect the monitor in cold weather. Show the envelope, bubble pouch, and insulation sheet if applicable.]

"To re-cap everything you will need for the activity assessment: programmed monitor that is to be worn on the hip, a blank log sheet with instructions, a list of key points on how to complete this protocol, another information sheet with additional details, the letter for classroom teacher, and the return envelope."

[Pause and allow the parents to go over the package.]

[Emphasize the bottom line of this protocol is to wear the monitor except for water activities and write down the minutes on the log.]

[Bring the parent's attention to the black rubber flap.]

"This little cap is to cover the USB port and blocks water from getting into the meter. It is now fully locked. Please do not touch or unlock this cap during data collection. Also do not stretch the black rubber flap because that will leave faulty data in the meter. Plus, this flap is not durable and is easy to break."

"Please remember to mail back the monitor and the log after 7 days."

[Schedule and confirm the data collection dates with the family and initialize the monitor. Make sure the battery is fully charged before giving it out.]

** Hand out the incentive when appropriate. It could be before or after data collection.

** Ideally the data collection is to be completed as close to the birthday visit as possible due to the battery life. If the subject misses the birthday visit, we will postpone data collection to after the mid-year visit. We allow a 12-month window for this protocol, which means the subject can wear the monitor anytime from 6 months prior to the birthday visit to 6 months after.

** In the scenario that the previous activity assessment happened around the mid-year visit, the next annual activity assessment should still be scheduled around the birthday visit.

** It is critical to encourage subject compliance that the sites make reminder phone calls or email communications on the 3rd or 4th day of assessment and answer questions from families.

** The English instructional materials are developed with a reading level around 8th grade. It is essential to keep the same readability when translated to other languages.

19.4 Accelerometer Distribution, Inventory and Tracking

- At the DCC

The DCC will order the accelerometers after finalizing the quantity needed at each clinic. The Actigraph® company will ship the monitors directly to the clinics located in the following cities:

US: Atlanta, GA; Augusta, GA; Denver, CO; Gainesville, GL; Seattle, WA

Finland: Oulu, Tampere, Turku

Germany: Munich

Sweden: Kristianstad, Helsingborg, Malmö

Whenever the clinic reports malfunctioning accelerometers, the DCC will assist the site with filing a repair or replacement request with the manufacturer (referred to as the RMA request by the manufacturer) and mail the faulty unit(s) to the manufacturer. The DCC will log the serial number of every accelerometer purchased and repaired.

The DCC will order accessories needed to operate the accelerometers and send to clinics in the above cities. Such accessories include the USB charging port, USB cable, accelerometer elastic belt material, and the belt buckle.

Three packaging and shipping materials are recommended for mailing the accelerometers, namely the purchase bubble pouch (www.uline.com, item# S-15689), padded envelope (www.uline.com, item# S-13944), and the pre-cut insulation sheet (www.uline.com, item # S-12789). The sites can order these materials using the TEDDY Supply Order Form.

The US sites can choose either to have the DCC prepare pre-filled FedEx airbills for returning the accelerometers to the clinics or to make the return mailing label locally. No label will be prepared for shipping the monitor to the families, but the US sites can use the DCC FedEx account to pay for the shipping. The European sites will make arrangements with their respective postal services and send quarterly shipping bills to the DCC (Susan Smith) for reimbursement.

**Choose “international priority” when shipping with FedEx between Europe and the U.S. or “2-day” if it is within the U.S. .

**FedEx strongly recommends detailed and adequate description on the shipping label in order to minimize any confusion or red flag regarding the accelerometer. <u>This is extremely important when shipping the device to the U.S.</u> Please <u>always</u> copy and paste the following paragraph on the shipping label:

"Accelerometer (= activity monitor). Non medical electronic device used to study the acceleration of body movements. For research use only."

- At the clinics

Upon receiving the shipment, the clinic staff needs to verify the quantity and notify the DCC whether or not the shipment is consistent with the invoice. Charge new accelerometers before initial use to check the battery quality. Whenever a broken monitor is identified, the clinic should report to the DCC and DCC will assist the site with filing a repair or replacement request with the manufacturer (referred to as the RMA request by the manufacturer) and mail the faulty unit(s) to the manufacturer.

Every clinic needs to have a local system to track the status and location of the monitor and activity log. The tracking system should contain, but not be limited to, the information below (some are also captured in the DCC data uploading system):

Meter Serial Number

TEDDY Local ID

TEDDY Subject ID

Subject Date of Birth

Data Collection Stat Date

Data Collection End Date

Initialization Date

Meter Fully Charged? If not, why

Participant Mailing Address

Date Sending the Data Collection Package (in person or by mail)

Date Reminder Call or Email Placed (ideally on the 3rd or 4th day of collection)

Expected Return Date of Meter

Date Meter Received at the Clinic

Date Re-Sending Return Envelope (or Box) (if the family loses the one given at the visit)

Date Reminding the Subject to Return the Meter (if meter not received at the clinic 7 days after collection)

Meter Data Download Date

Meter Data Download Staff Code

Date Log Received at the Clinic

Activity Log Entry Date

Activity Log Entry Staff Code

Meter Broken? If yes, record the condition

Date Sent Broken Meter to the manufacturer or the DCC

Is This a Repaired or Replacement Meter? If yes, date received (** replacement will be shipped from the manufacturer or the DCC)

If feasible, the sites will notify the long-distance family that a shipment is coming and use the tracking number to check if the package is delivered to the subject. It is optional to insure for each monitor,depending on the reliability of local postal service.

The sites need to contact the subjects by all possible means if the accelerometers are not received at the clinics 2 weeks after the completion of data collection. In the event that a monitor is not returned 3 months after data collection, it will be deemed as a lost piece and will need to be reported to the DCC with its serial number correctly indicated.

19.5 Data Management

19.5.1 Privacy & Confidentiality of Data

Data recorded on the accelerometer and the activity log are entered into a database at the clinical centers wherein the TEDDY subject is identified only by code – one code is issued by the DCC and another is a local code for the clinical center. Names, addresses and other personal information are not recorded in the databases, in keeping with considerations for privacy and confidentiality in all countries, and specifically with HIPAA requirements in the USA. The participant identification number will be used for record retrieval in the event of questions from the DCC or study investigators.

19.5.2 Site-Specific Data Management

Backup of the downloaded accelerometer data is routinely conducted to ensure the security of the data. Daily backup is preferred and back-up copies are stored in a location separate from the computer. Filled activity logs should be kept in the participant's file at the clinical centers following the IRB policy.

19.5.3 Quality Assurance Overview

Study-wide quality assurance procedures, and procedures to remedy deficiencies in quality measures, are discussed below.

Onsite Quality Assurance

Onsite quality assurance covers accelerometer operation, activity log review and online data entry and is coordinated by lead activity staff who oversees the overall data collection in each clinic.

- Every staff is expected to 1) check frequently the settings of the ActiLife program to make sure they are consistent with TEDDY's requirement (see Section 1.3.4); and 2) review the activity log soon after it is returned to the clinic and clarify questions or ambiguous information with the family as needed.
- The lead activity staff conducts periodic quality control observations of the physical activity protocol demonstration and random review of entered activity log. The Activity Assessment Introduction Observation Form (Appendix 19F) is designed to document information on the quality of protocol demonstration and to offer suggestions for improvement. This form is completed by the site lead activity person after observation. Upon completion of the observation, information is shared with the staff.

Checking of the Activity Log

The following items should be checked for each log received:

- Dates of data collection period
- Meter removal date and time at the end of data collection
- Wake-up time and bedtime for every day
- Durations of meter non-wear time

Checking of the Accelerometer Data

The sites are recommended to upload the accelerometer data (.gt3x file) to the DCC as soon as possible so that the DCC can archive the file and check for data quality. The ActiLife Lite edition automatically scans the downloaded data based on the pre-determined percentage, which will notify the sites of large gaps (null data, or Os) in the data which may indicate either a device failure or subject incompliance. The site should notify the DCC of any notification appeared upon downloading the .gt3x file.

19.6 Data Submission

The activity data transfer protocol is consistent in all TEDDY countries. The sites should retain a copy of the uploaded accelerometer data and archive the returned activity logs. The procedures to transfer accelerometer data and enter activity log online are described below separately.

** If you need to correct any data that has been entered, contact the DCC at teddy@epi.usf.edu

19.6.1 Enter Activity Log Online

** The Activity Log Consolidation form is not required prior to uploading the accelerometer data for reimbursement purpose.

** If the parent did not complete the log or the log was never returned to the clinic, the Activity Log Consolidation form can be left blank. However, the undone log should be marked in the Log Tracking System.

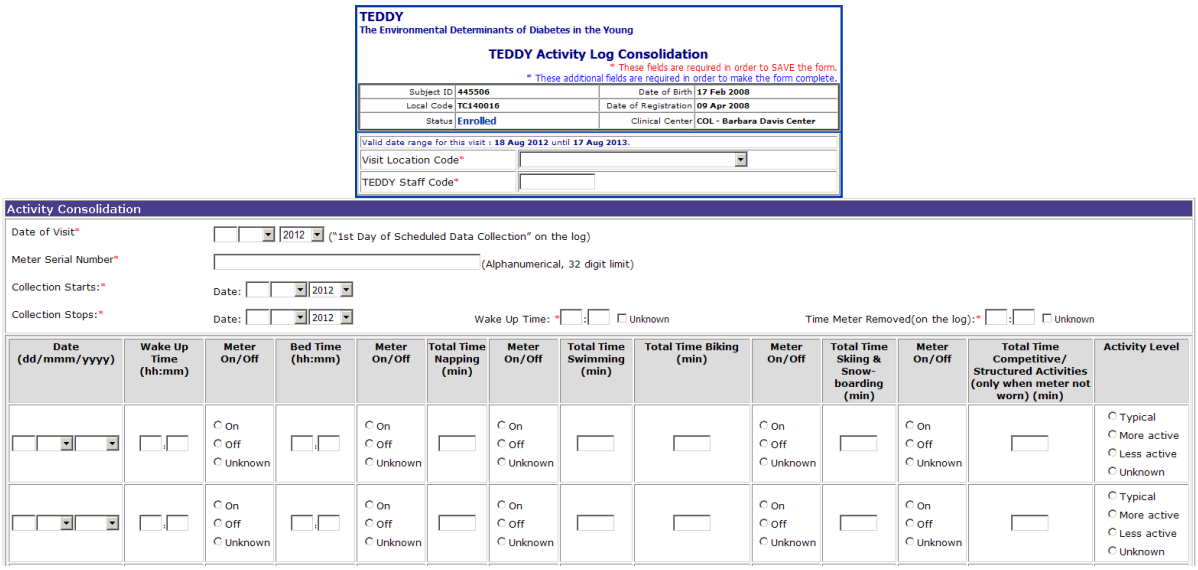
1. Log in to the TEDDY website.
2. Open the Participant's Details page for a given subject.
3. You will see an event "Activit Log Consolidation" listed under every annual test starting from Year 5. Locate the correct visit number and click "View/Edit/Print" to open the online form.

4. Red asterisks mark all fields required to save the form. Blue asterisks mark all fields required to identify this form as being completed.

   ** No future dates are allowed on this form.

   ** All the hourse are between 0-23 and all the minutes are between 0-59. Use "00:00" for midnight (12AM).

   Below is a screen shot of the old Consolidation form. A screen shot of the new Consolidation Form will be added after it is available.



5. The columns correspond to the order of questions on the activity log.
6. Once a date (first column on the left) is entered, the Activitly Level (last column on the right) must be indicated in order to save the form. In the new log, the wake up time and bed time are required once a date (first column on the left) is entered. **If the parent did not report a time, enter 99:99.
7. Each "Meter On/Off" column refers to the column to its left. For example, the "Meter On/Off" follwing "Total Time Biking" refers to the meter wearing status during biking. These columns will be removed in the new Consolidation Form.

** The "Meter On/Off" field must be indicated whenever the column to its left (i.e. "Wake Up Time", "Bed Time", "Total Time…") is filled in.

** If an acitivty did not take place, both "Total Time…" and "Meter On/Off" fields can be left blank. However, as long as one of the two fields is filled in, the other must be entered.

8. When working with the new online form, enter "Don't Know" for the last question on the log if 1) the parents are not sure if the child wore the meter overnight; or 2) the parents do not answer this question.
9. If more than seven days are recorded on the log, click the "Add Row" button to enter the extra day(s).
10. Click "Save" at the bottome of the page after all information is entered.

    ** Data recorded on the old log can be entered into the corresponding fields in the new online Consolidation Form. Use "unknown" for "Did child wear meter during sleep overnight?" if the answer is not clearly indicated on the old log.

11. The production of the activity plots references the wearing dates on the log, so filling out such information as soon as possible will greatly help prevent the non-wearing dates from getting plotted.

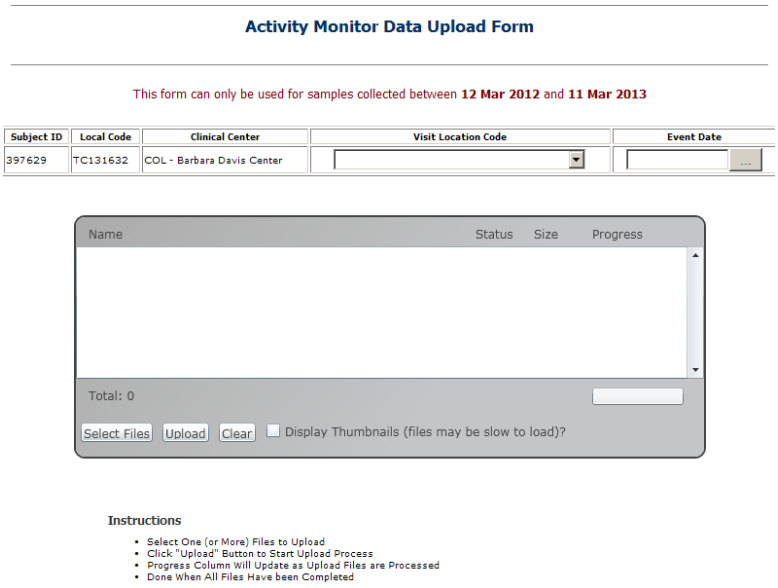
    If the wearing dates were not provided by the family, please try to determine using the best of your knowledge. If no date is found on the log, our program will work with the monitor data file alone, which sometimes will result in plotting the shipping movements.

19.6.2 Upload Accelerometer File

** The acclereomter data can only be uploaded after the Activity Log Consolidation form is completed.

1. Microsoft® Silverlight is the required software to upload accelerometer files. It can be downloaded from http://www.microsoft.com/silverlight/.
2. Log in to the TEDDY website.
3. Open the Participant's Details page for a given subject.
4. You will see an event "Activit Monitor Data Upload" listed under every annual test starting from Year 5. Locate the correct visit number and click "View/Edit/Print" to open the online form.

5. Enter Visit Location Code and Event Date. The "Event Date" refers to the date the monitor was received by the clinic.



6. Click "Select Files" and choose the file(s) you want to upload. The files will appear in the progress window.

   ** Make sure the file(s) to be uploaded are named following the correct naming schema which is "Subject ID_Local ID(starting date).gt3x". Any alphabet in the ID should be capitalized.

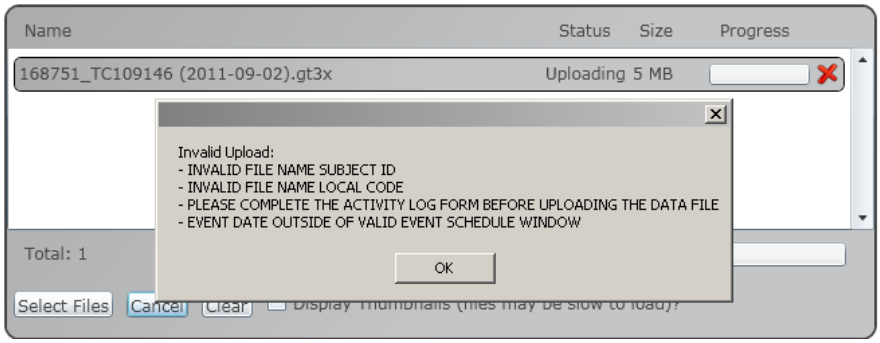
7. Click "Upload".

   ** An error message will appear if incorrect Subject ID or Local Code is detected. You will need to go back to the file folder and correct file names before reuploading.

   ** The system will check the IDs in every file name if multiple files are selected.

   ** The uploading speed may be limited by the large file size, client upload bitrate, and your physical location as the file is routed across the internet.

Subject ID	Local Code	Clinical Center	Visit Location Code	Event Date
397629	TC131632	COL - Barbara Davis Center	106 - TEDDY/DAISY Clinic	05-Sep-2011



8. Make sure to upload the file to the correct visit. The system is not able to check the date contained in the .gt3x file name, which means you will not receive an error message if a 6-year file labeled with correct Subject ID and Local Code is uploaded to the 7-year annual visit.
9. Notifiy the DCC at teddy@epi.usf.edu if a file was uploaded incorrectly. The DCC will document such incident and manually delete the incorrect file before allowing you to upload the correct one. The clinics can not remove uploaded files.
10. The DCC sends a status notification email to the file uploader within 24 hours of uploading. A successful upload notice looks like this:

TEDDY Activity Monitor File Status

FileName	Date Upload	Status
2015_12_21_113959_398530_203180 (2015-12-02).gt3x	22/Dec/2015	Uploaded Activity Monitor has **SUCCESSFULLY** been processed and imported into the data store.

19.6.3 Activity Plot

An activity plot is produced at every visit to boost retention. The plotting program randomly selects a day from the valid wearing days captured by the accelerometer and plots the activity levels from that day. This plot has no scale or reference level that can be used to evaluate a person's activity habit. It is merely a graphic presentation of some of the data from the monitor file. An example of the plot is shown in Appendix 19E.

** The dates on the log are used in producing the activity plot. If no monitor wearing date is indicated on the log, movements recorded during shipping may be deemed as valid data and be shown in the plot. If this happens, please notify the DCC and provide the dates of data collection so that the plot can be produced using data from an actual wearing date.

19.7 Data Tracking System

The TEDDY study is capturing attributes related to activity data that are late/missing or otherwise deficient in order to help with data analysis. The reasons why families submit these exceptional activity data are organized in drop-down boxes in each subject's record screen in the tracking system.

TEDDY MOO

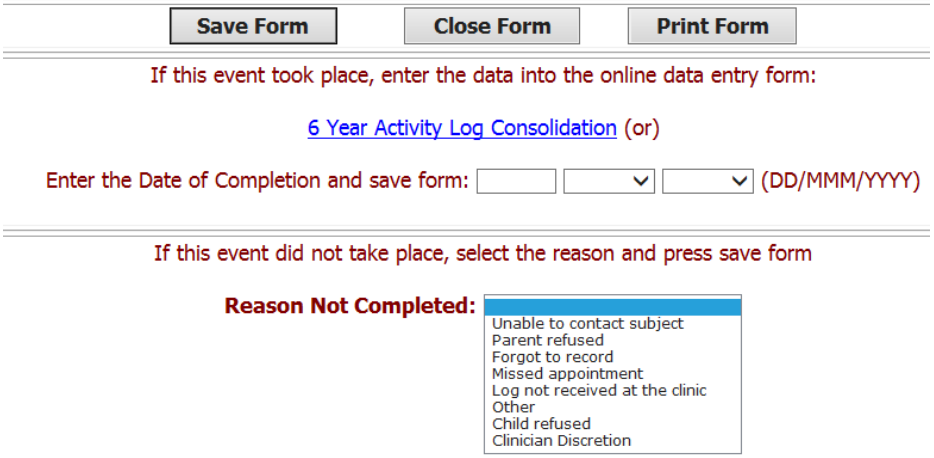
** To make a date change outside of the window, please contact the DCC at teddy@epi.usf.edu

19.7.1 Tracking System for Activity Log

It is required to complete the log tracking system prior to uploading the monitor data.

1. Log in to the TEDDY website.
2. Open the Participant's Details page for a given subject.
3. You will see an event "Activity Log Consolidation" listed under every annual test starting from Year 5. Click "Tracking" to open the tracking system for the activity log.

4. If the log has been returned to the TEDDY clinic, please enter "Date of Completion" and click "Save Form". The "Date of Completion" means the date on which the log is received at the TEDDY clinic.



** A link to the Activity Log Consolidation form is provided here for data entry.

5. If the log is not completed, please indicate a reason in the drop down memu and click "Save Form".

   Reason Not Completed

   - Unable to contact subject

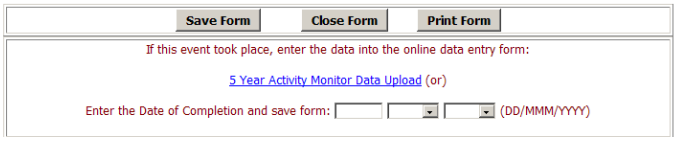
- Child refused
- Parent refused
- Forgot to record
- Missed appointment
- Log not received at the clinic
- Clinician discretion
- Other

19.7.2 Tracking System for Accelerometer Data

1. Log in to the TEDDY website.
2. Open the Participant's Details page for a given subject.
3. You will see an event "Activity Monitor Data Upload" listed under every annual test starting from Year 5. Click "Tracking" to open the tracking system for the monitor data.

Visit / Activity	Event Title	Visit Due Within	Completion Date	Last Modified Date	Task Status
Year 6 - Annual Test	Annual Questionnaire View/Edit/Print Tracking	01 Aug 2010 - 31 Jul 2011			
	Annual Questionnaire (2) View/Edit/Print Tracking	01 Aug 2010 - 31 Jul 2011	03 Mar 2011	14 Mar 2011	Complete
	Tracking form: Symptoms of Celiac Disease View/Edit/Print Tracking	01 Aug 2010 - 31 Jul 2011	05 Mar 2011	16 Mar 2011	Complete
	Activity Log Consolidation View/Edit/Print Tracking	01 Aug 2010 - 31 Jul 2011			
	Activity Monitor Data Upload View/Edit/Print Tracking	01 Aug 2010 - 31 Jul 2011			
	Physical Exam Form View/Edit/Print Tracking	01 Nov 2010 - 30 Apr 2011	05 Mar 2011	16 Mar 2011	Complete
	TEDDY Book Data Extraction - 2 To 5 Year View/Edit/Print Tracking	01 Nov 2010 - 30 Apr 2011	05 Mar 2011	16 Mar 2011	Complete

4. If the accelerometer data has been recorded, please enter "Date of Completion" and click "Save Form". The "Date of Completion" for the accelerometer data means the date on which data is downloaded from the monitor and saved on a local computer.

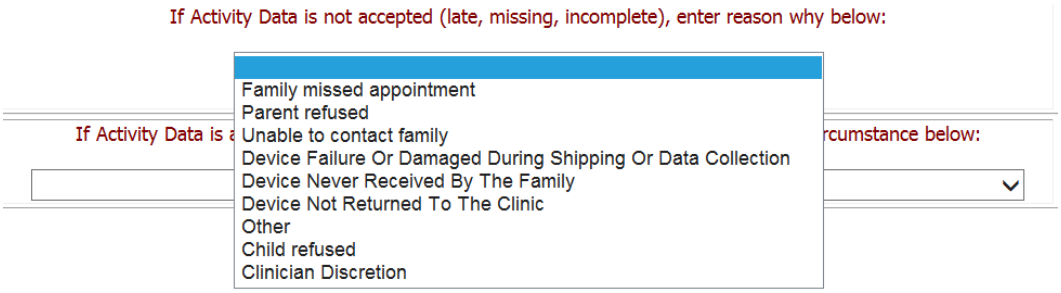


5. If the accelerometer data is not accepted, please indicate a reason in the drop down memu and click "Save Form".

Accelerometer data that are late or missing and INCOMPLETE, NOT ACCEPTED

- Family missed appointment
- Preant refused
- Child refused

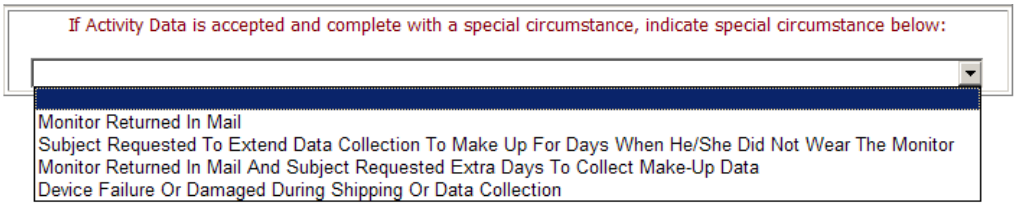
- Unable to contact family
- Device failure or damaged during shipping or data collection
- Device never received by the family
- Device not returned to the clinic
- Clinician discretion
- Other



6. If the accelerometer data is accepted and complete with a special circumstance, please indicate the circumstance in the drop down memu and click "Save Form".

Accelerometer data that is ACCEPTED, COMPLETE with special circumstances

- Monitor returned in mail
- Subject requested to extend data collection to make up for days when he/she did not wear the monitor
- Monitor returned in mail and subject requested extra days to collect make-up data
- Device failure or damaged during shipping or data collection



19.8 Frequently Asked Questions

Note Well: If none of these troubleshooting instrucitons work, notify the DCC before sending the monitor(s) in question to the DCC. Make sure to bubble wrap each monitor individually, pack them very carefully in the approved envelop or box, and insure each monitor for $400.

1. *Q: Do we need to do any checks of the monitor after receiving the shipment from the company?*

A: It is recommended to fully charge all monitors before initialization and distribution to the subjects.

2. *Q: What happens if the activity monitor comes in contact with a magnet?*

A: Nothing will happen. This device is immune to magnetic fields and other electromagnetic interference in accordance with FCC standards. In addition, security procedures associated with air travel or express mail (i.e., x-ray screening) do not adversely affect the data stored on the accelerometer.

3. *Q: What do we do if the LED light is not working properly?*

A: Notify the DCC and the DCC will assist you to file a RMA request for repair/exchange with the manufacturer.

4. *Q: What if I see a crack in the case of the accelerometer?*

A: Notify the DCC and the DCC will consult the company to see if repair/exchange is needed. If so, the DCC will assist you to file a RMA request.

5. *Q: Can the ActiLife software run on multiple computers?*

A: Yes, up to two computers at each clinic. An activation code is required to activate the ActiLife program after it is installed on a computer (desktop or laptop) that is operated under the Microsoft® Windows system. Only one usage of the activation code is allowed for every computer. Each site can use the activation code up to two times, meaning the software can run on two computers. If you want to run the program on a different computer, you need to first inactivate the program before installing and activating it on the destination computer. After successful activation, please remember to load the TEDDY Template file (available on the TEDDY website, Data Forms section, Physical Activity Assessment folder) and customize other settings (refer to the MOO section 19.3.4).

6. *Q: Can the ActiLife software be installed on a remote server?*

A: No. The software must be installed on a computer which will be physically connected to the accelerometers. Otherwise, the monitor will not be recognized by the program and no initialization or downloading can be done.

7. *Q: What if I have trouble initializing the activity monitor?*

A: Check that the battery is adequately charged. Try again by reconnecting the monitor to the computer and starting the ActiLife program. Sometimes it can take several tries to get a monitor to initialize. If problems persist, you can try rebooting the computer and even just setting that monitor aside and coming back to it if you have other monitors to work with.

8. *Q: What do you do when a monitor is not recognized at all by the ActiLife program - nothing happens when we try to initialize or download them?*

A: Make sure the battery is adequately charged. Check if the USB connection is working well. Try again by reconnecting the monitor to the computer. Keep in mind that, when using desktop computers, it is recommend connect the monitor directly to the rear USB ports instead of the ports on the side of the computer monitor. The rear ports are directly hard-soldered to the motherboard, and therefore it is less likely to lose current over a span of internal connecting cable. For laptops, there is no preferred port as there are all directly connected.

Sometimes it can take several tries to get a monitor to initialize depending on the mounting of the USB port. You can also try a different computer. Another common reason is that the

end of the USB cable is loosely connected to the computer or the accelerometer. Sometimes bending the cable multiple times may also break it, which may be invisible from the outside.

If the monitor still does not respond, contact the DCC as either the monitor may need to be sent in for repair or the USD cable is broken and you need a replacement.

9. Q: What does 'Current Address is zero' mean as an error message when downloading?

A: This message indicates that the monitor has not collected data. Other possible error messages resulting from the same problem are:

- There is no data to download from device {serial number}.
- The device is in reset mode.
- The device {serial number} has not started recording data.

This is not a bug, but in fact indicates that the device was never told to start collecting data.

10. Q: If a monitor gives the 'current address is zero' message at download, but we get the existing data off it, is there anything that needs to be done to the Actigraph before initializing it again for the next round of data collection?

A: See answers above. If you encounter problems extracting data from the monitor under normal circumstances, please contact the DCC and the DCC will obtain help from the company. The disclaimer is that the company will help only with normal usage. If the monitor is damaged or impaired, the DCC will help you to file a repair/exchange request with the manufacturer.

11. Q: What happens if the activity monitor does not download completely?

A: The monitor battery may be dead. Recharge the battery and try again. The data will not be lost. The major drain on the battery is from the download procedure. It is unlikely that a battery would go dead during the week that a monitor is collecting data.

12. Q: What if the USB charging port is broken?

A: Use another USB charging port. Inform the DCC if you need additional ports.

13. Q: What if you initialize more monitors than you use on a given day, and don't use them within the next 36-48 hours?

A: Simply re-initialize. DO NOT download anything. It's not necessary. Whatever data collected during idle time will be overwritten during re-initialization.

14. Q: How can you get out of the initializing or downloading process if you realize halfway through that you've done something wrong?

A: Once the initialization or downloading process has begun, it cannot be interrupted, so proceed to the end and then re-initialize or re-download.

15. Q: What if a subject forgets to wear the monitor?

A: The sites are expected to place reminder call or email during data collection. We will not ask a subject to repeat data collection if he/she forgot to wear the monitor for one or multiple days. If the parent contacts the clinic within the data collection week or before returning the

monitor and asks if the subject needs to make up for the missed day(s), we will permit that option given the subject is willing to wear the monitor for extra day(s). Subsequently, the clinic staff needs to remind the parent to complete the activity log during the extended time period and provide a prepaid labeled padded envelope to the family so that they can mail back the monitor.

16. Q: A subject forgot to put the monitor back on after bath (e.g. for 20 minutes, 2 hours or longer). Do I need to document it on the Activity Log?

A: No need to document such scenario on the Log or the Online Consolidation Form. It will be addressed in the data processing stage.

17. Q: A subject wore the monitor last time between mid-year visit and birthday visit (e.g.6.5-year and 7-year visits). When should the next data collection take place?

A: The next data collection should ideally be scheduled close to the next birthday visit, which would be the 7-year visit in the example.

18. Q: What if a subject forgets to return the monitor?

A: The clinic will contact the family if the monitor is not received 7 days after data collection. If needed, resend the return envelope with bubble pouch and insulation sheet (when applicable). A monitor not returned 3 months after data collection will be deemed as a lost piece and will need to be reported to the DCC with its serial number correctly indicated.

19. Q: What if the monitor serial number starts to wear off after multiple uses?

A: The sites should copy the serial number prior to the first use of every monitor and make a replacement sticker when the original one starts to wear off. Always maintain legible serial number as it is the ONLY identifier to match a monitor with a given subject.

20. Q: How do I remove the sticky residue from a sticker or a tape used on the monitor?

A: Try Goo-Gone® or a similar product that is safe for the polycarbonate case.

21. Q: How to best pretect the Lithium Ion battery in the monitor?

A: To maximally preserve the capacity of the lithium ion battery, it is recommended that monitors be stored in a fully charged state in low ambient temperatures. Devices remaining in storage should be recharged to this level every two to three months.

22. Q: Why could the date on the activity plot be outside of the data collection week? What to do if that happens?

A: The monitor may have captured a soniderable amount of movements during shipping. If you believe the date on a graph is incorrect, please email teddy@epi.usfu.edu or Jimin Yang or Martha Butterworth and include the dates of data collection.

Another action to help prevent this from happening is to indicate the activity monitor wearing dates in the online log consolidation form. The production of the activity plots references the wearing dates on the log, so filling out such information as soon as possible will greatly help prevent the non-wearing dates from getting plotted. If the wearing dates were not provided by the family, please try to determine using the best of your knowledge. If no date is found on the log, our program will work with the monitor data file alone, which sometimes will result in plotting the shipping movements.

TEDDY MOO

23. *Q: What are appropriate reasons for using the Clinician Discretion optionin in the tracking systems?*

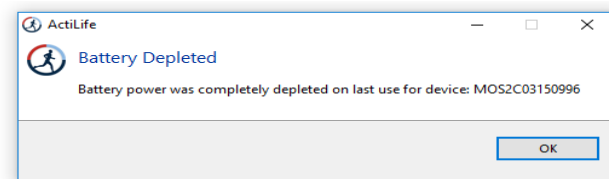
A: The TEDDY child or the parent is not able to complete other aspects of the protocol well. This could be due to a) the TEDDY Child having a medical/behavioral condition preventing them from being able to wear the belt; b) The TEDDY family experiencing challenges outside of TEDDY and the clinician feeling the accelerometer protocol may be too much of an additional burden at the time it is due. The clinician can also use discretion at a visit when the family is re-enrolling in TEDDY in order to not over-burden the family with too much at once.

24. *Q: What to do if I have not received the status notification email after uploading the monitor file?*

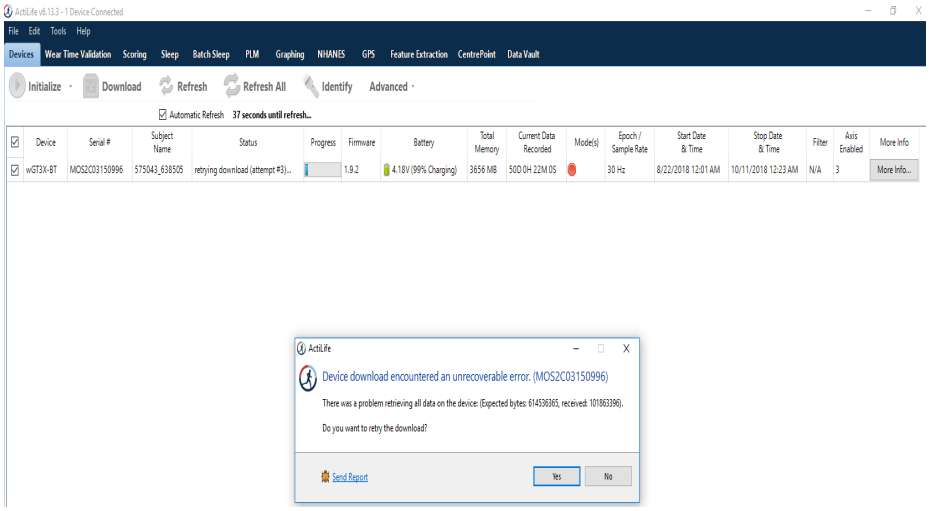
A: Please email teddy@epi.usf.edu with the subject ID and the name of the monitor data file.

25. *Q: What if the data can not be downloaded from the meter?*

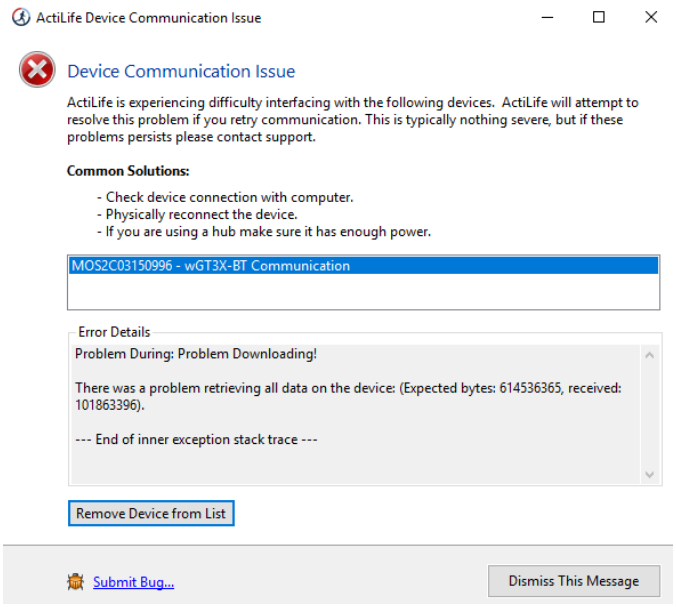
A: The following error messages may appear when you try to download the activity data from a monitor.



This message may appear after you click the "download" button.



This message may appear a few seconds after the download process is started.



This message may appear if you click "No" in response to the message above.

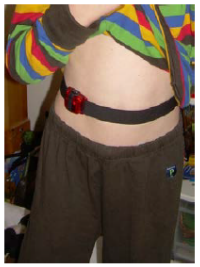
In this case, first to make sure the battery is fully charged. Second, try using a different USB cable to connect the monitor with the computer and downloading again. If this does not resolve the problem, please download the **Activity Monitor Data Recovery Tool** to help extract the data from http://actigraphcorp.com/support/software/device-data-rescuer/. This tool should be able to retrieve the data off of your device. Once the data has been extracted, take a look at the data in ActiLife to make sure everything looks fine. If the data seems to be normal, you can upload the .gt3x file as usual to the DCC and re-initialize the device for the next subject. If you aren't able to extract it, or the extracted data looks abnormal, please contact the DCC as we may need to send the device back to the company for repair.

19.9 Appendices

All appendices are listed in the order of English, Finnish, German, Spanish, and Swedish except for Appendix 19G which is available in English only.

Appendix 19A: Activity Log

	Date dd/mmm/yyyy	Wake Up Time	Bedtime	Times meter not worn *during sport activities*		Times meter not worn *during sport activities*	Did child wear meter during sleep overnight?
				1	2	3	
Day 1		:	:	_ _: _ _ to _ _: _ _	_ _: _ _ to _ _: _ _	_ _: _ _ to _ _: _ _	Yes No Don't Know
Day 2		:	:	_ _: _ _ to _ _: _ _	_ _: _ _ to _ _: _ _	_ _: _ _ to _ _: _ _	Yes No Don't Know
Day 3		:	:	_ _: _ _ to _ _: _ _	_ _: _ _ to _ _: _ _	_ _: _ _ to _ _: _ _	Yes No Don't Know
Day 4		:	:	_ _: _ _ to _ _: _ _	_ _: _ _ to _ _: _ _	_ _: _ _ to _ _: _ _	Yes No Don't Know
Day 5		:	:	_ _: _ _ to _ _: _ _	_ _: _ _ to _ _: _ _	_ _: _ _ to _ _: _ _	Yes No Don't Know
Day 6		:	:	_ _: _ _ to _ _: _ _	_ _: _ _ to _ _: _ _	_ _: _ _ to _ _: _ _	Yes No Don't Know
Day 7		:	:	_ _: _ _ to _ _: _ _	_ _: _ _ to _ _: _ _	_ _: _ _ to _ _: _ _	Yes No Don't Know
Day Meter Removed		:	Time Meter Removed :				



Problems / notes during data collection?

FOR OFFICE USE ONLY

Subject ID _____

Local ID _____

Meter Serial Number

_____

1st Day of Scheduled Data Collection (dd/mmm/yyyy)

_____

Date Meter Sent (dd/mmm/yyyy)

_____

Date Meter Received (dd/mmm/yyyy)

_____

☐ In Person ☐ By Mail

Date Log Entered (dd/mmm/yyyy)

_____

Activity Log

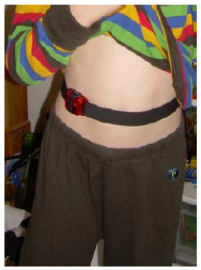
- Wear the activity meter for seven (7) days in a row as scheduled below.

_____after getting up
to
_____after getting up

- Keep the meter on your child at all times including sleeping.
- Water will break the meter. **Please take it off before your child swims, takes a shower or bath, and does anything that may get the meter wet.**
- **No need to record** the time of shower/bath.
- Write down any times when the meter was removed for sport activities.

- **Always remember to put the meter back on after taking it off**

	Päiväys pp/kkk/vvvv	Heräämis aika	Nukkumaa nmenoaika	Kirjaa, jos mittari ei ole vyötäröllä pelien tai muun liikunnan aikana		Kirjaa, jos mittari ei ole vyötäröllä pelien tai muun liikunnan aikana	Pitikö lapsi mittaria yöunen aikana?
				1	2	3	
Päivä 1		:	:	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Kyllä Ei En tiedä
Päivä 2		:	:	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Kyllä Ei En tiedä
Päivä 3		:	:	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Kyllä Ei En tiedä
Päivä 4		:	:	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Kyllä Ei En tiedä
Päivä 5		:	:	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Kyllä Ei En tiedä
Päivä 6		:	:	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Kyllä Ei En tiedä
Päivä 7		:	:	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Kyllä Ei En tiedä
Päivämäärä jolloin mittari poistettiin		:	**Mittarin irrottamis aika** :				



Ongelmat / muistiinpanot tietojen keräämisen aikana

AINOASTAAN TOIMISTOKÄYTTÖÖN

Tutkimushenkilön tunnus_____

Paikallinen tunnus_____

Mittarin sarjanumero

_____

1. tietojen keräämispäivä (pp/kkk/vvvv)

_____

Mittarin antopäivä (pp/kkk/vvvv)

_____

Mittarin palautuspäivä (pp/kkk/vvvv)

_____

☐ henkilökohtaisesti ☐ postitse

Toimintapäiväkirjan tietojen tallennuspäivä (pp/kkk/vvvv)_____

Toimintapäiväkirja

- Käytä aktiviteettimittaria seitsemän (7) päivää peräkkäin alla olevan aikataulun mukaisesti.

_____ylösnousun jälkeen

-

_____ylösnousun jälkeen

- Pidä mittari käytössä lapsella koko ajan, myös lapsen nukkuessa.
- Vesi rikkoo mittarin. **Ota se pois ennen kuin lapsi ui, ottaa suihkun tai kylvyn tai tekee jotain sellaista, jossa mittari voi kastua.**
- Suihkun/kylvyn/saunan kellonaikaa **ei kirjata.**
- Kirjaa kellonajat, jos mittari on ollut poissa vyötäröltä pelien tai muun liikunnan aikana.

- **Muista aina panna mittari takaisin sen jälkeen, kun se on otettu pois.**

	Datum TT/MM/JJJJ	Aufstehzeit	Bettgehzeit	Zeiten Messgerät abgelegt bei körperlichen Aktivitäten (Schwimmen etc.)			Wurde das Messgerät über Nacht getragen?	Sonstiges
				1	2	3		
Tag 1		:	:	__ __: __ __ bis __ __: __ __	__ __: __ __ bis __ __: __ __	__ __: __ __ bis __ __: __ __	Ja Nein Unbekannt	
Tag 2		:	:	__ __: __ __ bis __ __: __ __	__ __: __ __ bis __ __: __ __	__ __: __ __ bis __ __: __ __	Ja Nein Unbekannt	
Tag 3		:	:	__ __: __ __ bis __ __: __ __	__ __: __ __ bis __ __: __ __	__ __: __ __ bis __ __: __ __	Ja Nein Unbekannt	
Tag 4		:	:	__ __: __ __ bis __ __: __ __	__ __: __ __ bis __ __: __ __	__ __: __ __ bis __ __: __ __	Ja Nein Unbekannt	
Tag 5		:	:	__ __: __ __ bis __ __: __ __	__ __: __ __ bis __ __: __ __	__ __: __ __ bis __ __: __ __	Ja Nein Unbekannt	
Tag 6		:	:	__ __: __ __ bis __ __: __ __	__ __: __ __ bis __ __: __ __	__ __: __ __ bis __ __: __ __	Ja Nein Unbekannt	
Tag 7		:	:	__ __: __ __ bis __ __: __ __	__ __: __ __ bis __ __: __ __	__ __: __ __ bis __ __: __ __	Ja Nein Unbekannt	
Tag Gerät abgelegt		:	Messgerät abgelegt :					

Probleme / Anmerkungen während der Datenerfassung?

WIRD VOM STUDIENTEAM AUSGEFÜLLT

TEILNEHMER-ID _____

ÖRTLICHE ID _____

Seriennummer des Messgeräts

_____

1. Tag der geplanten Datenaufzeichnung (TT/MM/JJJJ)

_____

Datum der Zusendung des Messgeräts (TT/MM/JJJJ)

_____

Datum des Empfangs des Messgeräts (TT/MM/JJJJ)

_____

☐ Persönlich ☐ per Post

Datum des Protokolleintrags (TT/MM/JJJJ)

_____

Aktivitätsprotokoll

- Tragen Sie das Aktivitätsmessgerät an 7 aufeinanderfolgenden Tagen, wie unten angegeben.

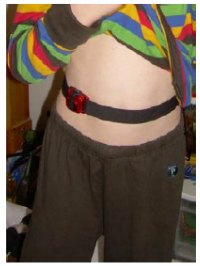
_____nach dem Aufstehen
bis:

_____nach dem Aufstehen

- Lassen Sie Ihr Kind das Gerät ständig tragen, auch beim Schlafen.
- Wasser beschädigt das Messgerät! **Bitte nehmen Sie es ab, bevor Ihr Kind schwimmen geht, duscht , badet oder andere Aktivitäten ausübt, bei denen das Messgerät nass werden könnte.**
- Die Zeiten dafür müssen nicht notiert werden.
- Notieren Sie die Gesamtzeit für alle sportlichen und körperlichen Aktivitäten bei denen das Gerät abgenommen wurde!
- Denken Sie immer daran, das Messegerät nach dem Abnehmen wieder anzulegen!

	Fecha dd/mmm/aaaa	Hora de levantarse	Hora de acostarse	Tiempo que no se utilizó el monitor durante actividades deportivas		Tiempo que no se utilizó el monitor durante actividades deportivas	¿Utilizo su hijo/a el monitor durante la noche?
				1	2	3	
Día 1		:	:	__:__ to __:__	__:__ to __:__	__:__ to __:__	Sí No No se
Día 2		:	:	__:__ to __:__	__:__ to __:__	__:__ to __:__	Sí No No se
Día 3		:	:	__:__ to __:__	__:__ to __:__	__:__ to __:__	Sí No No se
Día 4		:	:	__:__ to __:__	__:__ to __:__	__:__ to __:__	Sí No No se
Día 5		:	:	__:__ to __:__	__:__ to __:__	__:__ to __:__	Sí No No se
Día 6		:	:	__:__ to __:__	__:__ to __:__	__:__ to __:__	Sí No No se
Día 7		:	:	__:__ to __:__	__:__ to __:__	__:__ to __:__	Sí No No se
Día de quitarse el medidor		:	**Hora de quitarse el medidor** :				

¡GRACIAS!



Problemas/observaciones durante la obtención de datos

PARA USO EXCLUSIVO DE LA OFICINA

ID del sujeto _____

ID local:_____

Número de serie del medidor

_____

1er día de la obtención de datos programada (dd/mmm/aaaa)

_____

Fecha de envío del medidor (dd/mmm/aaaa)\

_____

Fecha de recepción del medidor (dd/mmm/aaaa)

_____

☐ personalmente ☐ por correo

Fecha de ingreso del registro (dd/mmm/aaaa)

_____

Registro de Actividades

- Use el medidor de actividad durante siete (7) días seguidos, según el siguiente cronograma.

____después de levantarse
hasta

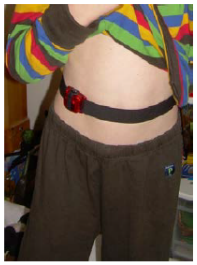
____después de levantarse

- Mantenga el medidor colocado en su hijo todo el tiempo, incluso mientras duerme.
- El agua descompone el medidor. **Quíteselo antes de que su hijo nade, tome una ducha o un baño o haga algo que pueda hacer que el medidor se moje.**
- **No es necesario** indicar el tiempo que se toma durante el baño o ducha.
- Anote el tiempo total cuando el monitor no fue utilizado durante actividades deportivas.

- Siempre recuerde volver a ponerse el medidor después de quitárselo.

	Datum år/månad/dag	Vaknade	Sängdags	Ifylls endast om Actigrafen inte bärs		Ifylls endast om Actigrafen inte bärs	Hade barnet mätaren på under natten?
				1	2	3	
Dag 1		:	:	_ _:_ _ till _ _:_ _	_ _:_ _ till _ _:_ _	_ _:_ _ till _ _:_ _	Ja Nej Vet inte
Dag 2		:	:	_ _:_ _ till _ _:_ _	_ _:_ _ till _ _:_ _	_ _:_ _ till _ _:_ _	Ja Nej Vet inte
Dag 3		:	:	_ _:_ _ till _ _:_ _	_ _:_ _ till _ _:_ _	_ _:_ _ till _ _:_ _	Ja Nej Vet inte
Dag 4		:	:	_ _:_ _ till _ _:_ _	_ _:_ _ till _ _:_ _	_ _:_ _ till _ _:_ _	Ja Nej Vet inte
Dag 5		:	:	_ _:_ _ till _ _:_ _	_ _:_ _ till _ _:_ _	_ _:_ _ till _ _:_ _	Ja Nej Vet inte
Dag 6		:	:	_ _:_ _ till _ _:_ _	_ _:_ _ till _ _:_ _	_ _:_ _ till _ _:_ _	Ja Nej Vet inte
Dag 7		:	:	_ _:_ _ till _ _:_ _	_ _:_ _ till _ _:_ _	_ _:_ _ till _ _:_ _	Ja Nej Vet inte
Dag Actigrafen avtagen		:	Tid Actigrafen avtagen :				

TACK FÖR HJÄLPEN!



Problems / iakttagelser under datainsamlingen?

Skriv ej här

Subject ID _____

Local ID _____

Actigrafens serienummer

_____

Första dagen för datainsamling (år-mån-dag)

_____

Datum då Actigrafen skickades (år-mån-dag)

_____

Datum då Actigrafen mottogs(år-mån-dag)

_____

☐ personligen ☐ med post

Datum då loggen fylldes i (år-mån-dag)

_____

Aktivitetslogg

- Bär Actigrafen sju (7) dagar i rad enligt schemat nedan.

_____efter uppstigning
till
_____efter uppstigning

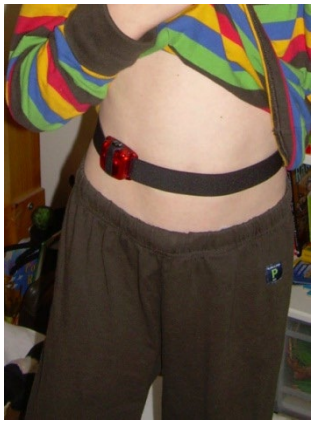
- Låt barnet bära Actigrafen hela tiden, även under sömn.
- Actigrafen förstörs av vatten. **Ta av den innan barnet simmar, duschar, badar eller gör något som kan orsaka att dosan blir våt.**
- Tid för dusch och bad behöver inte registreras.
- Ange den totala tiden för sportaktiviteter utförda **utan att ha burit** Actigrafen.

- **Kom alltid ihåg att sätta på Actigrafen igen efter att ha tagit av den**

Appendix 19B. Meter Wearing Key Points

TEDDY Activity Meter Instructions

1. Plan to wear the meter on the dates set by you and the TEDDY office. The meter is programmed to record on those days.
2. On day 1, place the meter on top of your child's right hip as shown in the picture. It can be worn on top of light clothing like a T shirt or in contact with skin. Please make the belt tight enough not to flop.
3. Keep the meter on your child during the day and night for 7 continuous days.
4. **Please do not get the meter wet. Water will damage it.**



You should mark on the log…

- The dates when the meter was worn
- The hours that the meter was taken off due to sport activities such as swimming and competitive/structured sports
- Time spent sleeping
- Whether your child wore the meter during sleep overnight

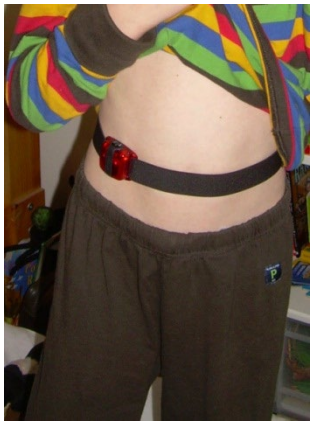
You should also…

- Fill in and give the letter about the activity meter to your child's teacher as needed.
- Return the activity meter, belt and completed log **as soon as possible** after the 7 day period.
- **Do not let anyone else wear it.**
- Do not forget to put it back on after taking it off.

If you have any questions or problems with the meter or log, please call TEDDY at _____.

TEDDY-aktiviteettimittarin ohjeet

1. Suunnittele mittarin käyttö päiville, jotka sovit TEDDY-tutkimuksen henkilökunnan kanssa. Mittari on ohjelmoitu tallentamaan tiedot noina päivinä.
2. Aseta mittari ensimmäisen mittauspäivän aamuna lapsesi oikean lonkan yläpuolelle kuvassa esitetyllä tavalla. Sitä voidaan käyttää kevyen vaatetuksen (esim. T-paita) päällä tai suoraan iholla. Kiristä vyötä riittävästi, jotta mittari ei heilu.
3. Pidä mittari lapsella päivällä ja yöllä seitsemän peräkkäisen päivän ajan.



4. **Älä altista mittaria kosteudelle. Vesi tuhoaa sen.**

<u>Sinun pitäisi merkitä toimintapäiväkirjaan…</u>

- Päivämäärät, jolloin mittaria käytettiin.
- Tunnit, jolloin mittari otettiin pois uinnin tai vesileikin ajaksi.
- Nukkumiseen, päiväuniin, pyöräilyyn, lasketteluun ja lumilautailuun käytetty aika - varmista, että mittari on lapsella käytössä noina aikoina.
- Maininta siitä, onko lapsesi aktiviteettitaso tyypillinen kirjaamispäivinä.

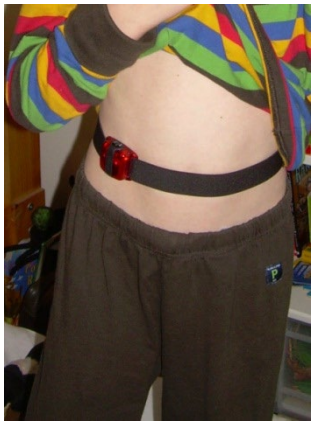
<u>Sinun pitäisi myös…</u>

- Merkitä peleihin ja ohjattuun liikuntaan (ks. lista monisteessa ‘Fyysistä aktiivisuutta mittaava TEDDY-mittari’) käytetty kokonaisaika jos mittari ei ollut päällä niiden aikana.
- Täyttää ja antaa aktiviteettimittarista kertova kirje lapsen päivähoidon henkilökunnalle/opettajalle tarvittaessa.
- Palauttaa aktiviteettimittari, vyö ja täytetty toimintapäiväkirja **mahdollisimman pian** seitsemän päivän jakson päätyttyä.
- **Älä anna kenenkään muun käyttää mittaria.**
- Älä unohda panna sitä takaisin sen jälkeen, kun se on otettu pois.

Jos sinulla on mittariin tai toimintapäiväkirjaan liittyviä kysymyksiä tai ongelmia, soita TEDDY-tutkimuksen henkilökunnalle numeroon _____.

Anleitung zum TEDDY-Aktivitätsmessgerät

1. Das Messgerät soll an den Tagen getragen werden, die von Ihnen und TEDDY festgelegt wurden. Das Messgerät wurde so programmiert, dass es an diesen Tagen aufzeichnet.
2. Befestigen Sie das Messgerät am Morgen des ersten Tags wie auf dem Bild über der rechten Hüfte Ihres Kindes. Es kann über einem dünnen Kleidungsstück, z. B. einem T-Shirt, oder direkt auf der Haut getragen werden. Der Gurt muss so eng anliegen, dass er nicht verrutschen kann.



3. Das Messgerät soll von Ihrem Kind an 7 aufeinanderfolgenden Tagen tagsüber und nachts getragen werden
4. **Das Messgerät darf nicht nass werden. Es wird durch Wasser beschädigt.**

<u>Im Protokoll muss festgehalten werden…</u>

- Das Datum der Tage, an denen das Messgerät getragen wurde.
- Die Stunden, für die das Messgerät bei sportlichen Aktivitäten wie zum Beispiel Schwimmen abgelegt wurde.
- Schlafzeiten (auch Mittagsschlaf)Ob das Gerät über Nacht getragen wurde.

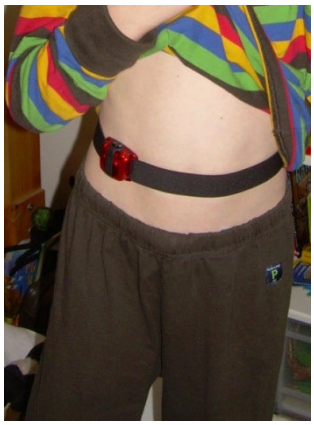
<u>Sie sollten auch...</u>

- gegebenenfalls das Erklärungsschreiben für Lehrer/ Trainer bezüglich des Aktivitätsmessgeräts ausfüllen und dem Lehrer Ihres Kindes aushändigen.
- Das Aktivitätsmessgerät, den Gürtel und das ausgefüllte Protokoll nach den 7 Tagen **so bald wie möglich** zurückzugeben
- **Es darf von keinen anderen Personen getragen werden.**
- Vergessen Sie nicht, es nach dem Abnehmen wieder anzulegen.

Sollten Sie Fragen oder Probleme mit dem Messgerät haben, rufen Sie bitte TEDDY unter 0800-3383339 an.

Instrucciones del medidor de actividad de TEDDY

1. Planee usar el medidor en las fechas acordadas por usted y la oficina de TEDDY. El medidor está programado para grabar en esos días.
2. En la mañana del día 1, coloque el medidor encima del lado derecho de la cadera de su hijo, como se muestra en la imagen. Puede usarse por encima de ropa ligera, como una camiseta, o en contacto directo con la piel. Ajuste el cinturón lo suficiente de modo que no se voltee.
3. Mantenga el medidor colocado en su hijo, día y noche, durante 7 días continuos.
4. **No moje el medidor, ya que el agua lo dañará.**



Debe marcar en el registro:

- Las fechas en qué se usó el medidor.
- Las horas que se quitó el medidor debido a natación y juegos con agua.
- El tiempo que pasó durmiendo, tomando una siesta, andando en bicicleta, practicando esquí de descenso y *snowboarding*; asegúrese de ponerse el medidor en todos esos momentos.
- Si los niveles de actividad del niño fueron los habituales durante los días de registro.

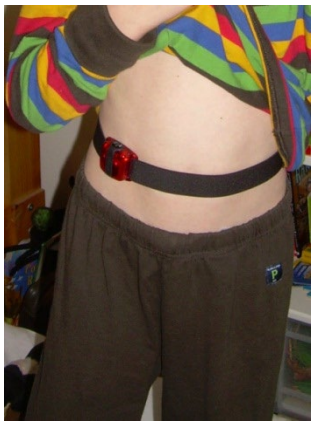
También debe:

- Indicar el tiempo total de una actividad estructurada o competitiva listada en *Medidor de actividad física de TEDDY: Preguntas y Respuestas* si se quita el medidor durante la actividad
- Llenar y entregar la carta sobre el medidor de actividad al maestro de su hijo, según sea necesario.
- Devolver el medidor de actividad, el cinturón y el registro completo **lo antes posible** después del período de 7 días.
- **No permitir que nadie más se lo ponga.**
- No olvidar ponérselo después de habérselo quitado.

Si tiene preguntas o problemas con el medidor o el registro, llame a TEDDY al _____.

Instruktioner TEDDY Fysisk Aktivitet

1. Bär Actigrafen under den period som ni och er TEDDY-sköterska har kommit överens om. Actigrafen är programmerad att samla in data under dessa dagar.
2. Actigrafen ska placeras på barnets högra höft (se bild). Detta görs på morgonen dag 1. Bältet med dosan kan bäras ovanpå lätta kläder (t.ex. T-shirt) eller direkt på huden. Se till så att bältet sitter så pass nära kroppen så att dosan inte hoppar runt.
3. Ditt barn ska bära Actigrafen dygnet runt, 7 dagar i följd.
4. **Dosan får inte komma i närheten av vatten. Vatten kan skada Actigrafen.**



Vad som ska antecknas i dagboken…

- Datum när Actigrafen burits.
- De timmar som Actigrafen togs av på grund av att simning, vattenlek, dusch/bad.
- Hur länge barnet sov, cyklade, åkte skidor (utför) eller snowboard. Bär dosan vid denna typ av aktivitet men notera även hur länge de utfördes.
- Om ditt barns aktivitetsnivå var normal eller ej under mätperioden.

Du ska också…

- Anteckna i loggen om Actigrafen togs av i samband med deltagande i någon typ av sportaktivitet (se lista FAQ TEDDY aktivitetsmätare). Ange även totaltiden för dessa aktiviteter.
- Lämna/skicka tillbaka Actigrafen, bälte och ifylld dagbok så fort som möjligt, efter det att mätningen är avslutad.
- **Inte låta inte någon annan bära Actigrafen.**

För att undvika att glömma dosan – ha den alltid på, förutom vid vattenaktiviteter!

Om ni har några frågor eller problem med Actigrafen eller dagboken, ring då till er TEDDY-sköterska.

Appendix 19C. Meter Q&A

TEDDY Physical Activity Meter Q&A

Here is more information to help you with the physical activity data collection.

**If at any time you have questions, please call the TEDDY Center at: (local number)

Please try not to lose or damage the meter. However, if you do lose or damage the meter, please call the TEDDY staff immediately. We will not charge you to replace or repair it. **We would still need you to return the meter even if it is broken. Should this happen, we will send your child another activity meter and reschedule the 7-day activity monitoring.

**If your meter accidentally, gets wet, damaged or lost, please call the TEDDY Study at: (local number)

- What is the Actigraph Meter?

The activity meter is a small, lightweight monitor worn around the waist on a belt. It measures physical activity by recording all of your child's movements.

This meter is LEAD FREE. It does not emit wireless signal or make sound. Magnetic materials will not affect it. Wearing it WILL NOT interfere with your child passing through security check points such as the ones in the airport.

This meter is not waterproof. The black rubber strap on the front of the meter is to block liquids from getting into the inside of the monitor. **Please make sure that the black rubber strap stays in place at all times and do not play with it.**

On the back of your child's activity meter is a number. This will be the same number that is on your child's activity log. Please leave the sticker on the meter.

- How to wear the activity meter?

Wear the meter above the right hip. To help collect good data, the meter should not flop around, but should fit snugly. Please do not have your child wear the meter on top of thick clothing like a sweater or a coat. It does not matter which side of the meter is facing up.

- Should my child wear the activity meter all the time?

Please have your child wear the meter for the full 7 days. However, please remove the meter for water activities like bathing, swimming and water parks. Also, try to keep the meter dry from the rain. The meter is durable so do not worry about it getting damaged during your child's usual activities even if it includes things like contact sports (soccer, rugby, etc.). It is important for us to measure your child's activity during these times. Wearing the meter during activities like these will not injure your child or other children. However, if you are concerned about this, it is fine to ask your child to remove the meter during contact sports.

- When should my child start wearing the meter?

Please have your child put the meter on right after he or she wakes up on the first day of your log. The meter will start by itself. On Day 8, your child should take off the meter when they wake up. This will help make sure we have enough data to analyze your child's activity level. Please follow the wearing schedule listed on the front of the activity log as much as possible.

- What about when my child is at school?

Please encourage your child to wear it at school. We provide you a letter that explains to the teachers why your child is wearing the meter. You should fill in the relevant details of the letter. We understand that you may not always know if your child has taken the activity meter off during school hours. It would be helpful if you could ask your child if he/she took the meter off at school for any reason, and record this on the log.

- What are the meter lights for?

There is one green and one red LED light on the meter. The green light will not flash before or during data collection. The red light will flash when technical errors happen. Please see the table below and contact the TEDDY clinic if the red light flashes.

No green or red light	Meter is collecting data.
Red light on, 2 flashes at a time	Battery is low. Still collecting data.
Red light on, 3 flashes at a time	Battery level is very low and is about to die. Keep wearing the meter.

Please do not attempt to open the meter to check for battery level or replace battery.

- What if the black rubber strap fell off the meter and the USB port is exposed?

The USB port cover should stays in all the time. DO NOT play with it during data collection. If you notice the cover has fallen off, use the edge of a coin to lock the cap by twisting it clockwise. (A flat head screwdriver may break the plastic.)

If the black rubber strap breaks completely and the cap cannot cover the USB port anymore, please keep wearing the monitor and be extremely careful not to let water get into the monitor. A piece of tape over the opening will help keep water out of the meter.

Notify the TEDDY staff of the broken strap when returning the monitor.

- What is the log for?

The log helps us better analyze the raw data that we get from the activity meter. We ask you to record the time spent sleeping and times when the meter is removed due to water activities (such as swimming) or other sport activities.

If your child took off the activity meter when participating in the following competitive and/or structured activities, please write down the *total duration (total minutes)* in a day. You do not need to specify the duration of every activity if there were more than one. No need to record an activity if it is not listed.

Physical Education Class (P.E.); Track and Field; Ball games (any sport played with a ball, such as American football, touch football, soccer, basketball, baseball, softball, tennis, badminton, field hockey, ice hockey, table tennis, handball, floor ball, golf, polo, water polo, lacrosse, etc); Cheerleading; Gymnastics; Wrestling; Fencing; Skating (including figure skating and short track); Other snow sports besides downhill skiing and snowboarding; Rollerblading; Dancing; Martial Arts; Surfing; Rock Climbing (indoor or outdoor); Horseback riding (including jockeying)

- What will happen to the information collected on the activity meter and log?

The TEDDY Study will treat information gathered by this meter in strict confidence in accordance with the TEDDY study protocol. The information you provide will be shared solely among study investigators and will not be released in any way that enables you to be identified.

- When should I return the activity meter and completed log?

It is very important that the meter be returned promptly after the seven (7) wearing days.

Fyysistä aktiivisuutta mittaava TEDDY-mittari

Tässä on lisätietoja, jotka auttavat fyysisen aktiivisuuden tietojen keräämisessä.

**Jos sinulle tulee kysyttävää, ota yhteyttä TEDDY-henkilökuntaan numeroon_____.

Yritä pitää mittari tallessa ja kunnossa. Jos mittari kuitenkin katoaa, kastuu tai vaurioituu muuten, soita TEDDY-tutkimuksen henkilökunnalle mahdollisimman pian numeroon_____. Sen vaihtaminen tai korjaaminen on maksutonta. **Mittari täytyy kuitenkin palauttaa, vaikka se olisi rikki. Mikäli näin tapahtuu, lähetämme lastasi varten toisen aktiviteettimittarin ja ajoitamme uudelleen 7-päiväisen aktiviteettien tarkkailujakson.

- Mikä on Actigraph-mittari?

Aktiviteettimittari on pieni, kevytpainoinen monitori, jota käytetään vyötärölle asetetussa vyössä. Se mittaa fyysistä aktiivisuutta kirjaamalla kaikki lapsesi liikkeet.

Mittari on LYIJYTÖN. Se ei lähetä langattomia signaaleja eikä siitä lähde ääntä. Magneettisilla materiaaleilla ei ole siihen vaikutusta. Sen käyttäminen EI aiheuta häiriötä, kun lapsi kulkee turvatarkastuspisteiden läpi (esim. lentokentällä).

Mittari ei ole vedenpitävä. Etupuolella olevan mustan kumihihnan tarkoituksena on estää nesteiden pääsy mittarin sisään. **Varmista, että mustat kumihihnat pysyvät paikoillaan kaikkina aikoina ja että sillä ei leikitä.**

Lapsesi aktiviteettimittarin takana on numero. Tämä on sama numero kuin lapsesi aktiviteettipäiväkirjassa. Älä irrota tarraa mittarista.

- Kuinka aktiviteettimittaria käytetään?

Käytä mittaria oikean lonkan yläpuolella. Tietojen keräämisen helpottamiseksi mittari ei saisi heilua vaan sen pitäisi istua iholla napakasti. Huolehdi, ettei lapsesi käytä mittaria paksun vaatetuksen (villapusero tai takki) päällä. Kumpi tahansa mittarin puolista voidaan asettaa suuntautumaan ylöspäin.

- Pitäisikö lapseni käyttää aktiviteettimittaria jatkuvasti?

Anna lapsesi käyttää mittaria täydet seitsemän päivää. Irrota mittari kuitenkin aktiviteeteissa, joissa se altistuu vedelle (suihku, kylpy, uinti, vesipuistot). Pyri myös pitämään mittari kuivana sateen aikana. Mittari on kestävä, joten sinun ei tarvitse pelätä sen vaurioituvan lapsen normaaleissa aktiviteeteissa, vaikka niihin kuuluisi kontaktiurheilulajeja (jalkapallo, amerikkalainen jalkapallo, jääkiekko, jne.). On tärkeää mitata lapsesi aktiviteetti näiden aikana. Mittarin käyttäminen tällaisten aktiviteettien aikana ei vahingoita lastasi tai muita lapsia. Jos olet kuitenkin huolestunut tästä, voit pyytää lastasi irrottamaan mittarin kontaktiurheilun ajaksi.

- Milloin lapseni pitäisi alkaa käyttää mittaria?

Pyydä lastasi panemaan mittari vyötärölle mittausjakson ensimmäisenä päivänä heti heräämisen jälkeen. Mittari käynnistyy itsestään. Mittari pitäisi irrottaa lapselta 8. päivänä heräämisen jälkeen. Näin varmistamme, että meillä on tarpeeksi tietoja lapsesi aktiviteettitason analysoimiseen. Noudata mahdollisimman tarkasti käyttöaikataulua, joka on näkyvissä aktiviteettipäiväkirjan etupuolella.

- Entä ajat, jolloin lapseni on päivähoidossa tai koulussa?

Kannusta lastasi käyttämään mittaria koulussa. Annamme sinulle kirjeen, jossa selitetään päivähoidon henkilökunnalle/opettajalle, miksi lapsesi käyttää tätä mittaria. Sinun pitäisi täyttää kirjeeseen vielä henkilötiedot. Ymmärrämme, että et kenties aina tiedä, onko lapsesi ottanut aktiviteettimittarin pois koulupäivän aikana. Suosittelemme, että kysyt lapseltasi, ottiko hän mittarin pois /päivähoidossa/koulussa jostakin syystä, ja kirjaat tämän toimintapäiväkirjaan.

- Mitä mittarin valot tarkoittavat?

Mittarissa on yksi vihreä ja yksi punainen LED valo. Vihreävalo ei vilku ennen eikä tietojen keräämisen aikana. Punainen valo vilkkuu teknisen ongelman sattuessa. Katso alla oleva taulukko ja ota yhteyttä TEDDY – klinikalle, jos punainen valo vilkkuu.

Ei vihreää tai punaista valoa.	Mittari kerää tietoja.
Punainen valo päällä, 2 välähdystä kerrallaan.	Pariston virta on alhainen. Mittari kerää yhä tietoja.
Punainen valo päällä, 3 välähdystä kerrallaan.	Pariston virta on lähes lopussa. Pidä mittaria edelleen vyötäröllä, se kerää yhä tietoja

Älä yritä avata mittaria pariston virtatason tarkastamista tai pariston vaihtamista varten.

- Mitä tapahtuu, jos USB-porttia suojaava musta kuminauha putoaa mittarista ja portti tulee näkyviin?

USB-portin suojan pitäisi olla paikoillaan koko ajan. ÄLÄ anna lapsesi leikkiä sillä tietojen keräämisen aikana. Jos huomaat, että suoja on pudonnut, lukitse se kiertämällä sitä kolikolla myötäpäivään. (Litteäpäinen ruuvimeisseli voi rikkoa muovin.)

Jos musta kuminauha rikkoutuu täysin eikä suoja enää peitä USB-porttia, anna lapsesi jatkaa mittarin käyttämistä. Pyydä häntä kuitenkin olemaan äärimmäisen varovainen, jotta laitteeseen ei pääse vettä. Teipin pala aukon päällä auttaa pitämään veden pois mittarista.

Mainitse TEDDY-henkilökunnalle rikkoutuneesta hihnasta, kun palautat mittarin.

- Mikä on toimintapäiväkirjan tarkoitus?

Päiväkirjan avulla on mahdollista analysoida paremmin tietoa, jota saamme aktiviteettimittarista. Pyydämme sinua kirjaamaan nukkumaanmeno- ja heräämisajat sekä kellonajat, jolloin mittaria ei pidetty vyötäröllä vesiaktiviteettien (kuten uimisen), pelien tai muun ohjatun liikunnan aikana.

Jos lapsesi otti mittarin pois päältä osallistuessaan seuraaviin peleihin ja/tai ohjattuun liikuntaan merkitse ylös niihin käytetty liikunnan kokonaisaika (minuuteissa) päivän aikana. Sinun ei tarvitse eritellä jokaisen aktiviteetin kestoaikaa erikseen jos enemmän kuin yksi. Jos aktiviteettia ei ole listattu alla sitä ei tarvitse merkitä.

Liikuntatunti, yleisurheilu, pallopelit (esim. jalkapallo, amerikkalainen jalkapallo, touch football, koripallo, baseball, pesäpallo, tennis, sulkapallo, jääkiekko, jääpallo, pöytätennis, käsipallo, salibandy, golf, polo, vesipallo, lacrosse), cheerleading, voimistelu, paini, miekkailu, luistelu (esim. kauno- tai pika-), muu talviurheilu kuin laskettelu tai lumilautailu, rullaluistelu, tanssi, martial arts (esim. tae wan do, judo), surffaus, kiipeily (sisällä tai ulkona), ratsastus.

Pyydämme sinua lisäksi mainitsemaan, onko aktiviteettitaso tyypillinen, aktiivisempi tai vähemmän aktiivinen aikana, jolloin lapsesi käyttää aktiviteettimittaria.

- Mitä tapahtuu aktiviteettimittarin ja toimintapäiväkirjann avulla kerätyille tiedoille?

TEDDY-tutkimuksessa käsitellään tällä mittarilla kerättyjä tietoja ehdottoman luottamuksellisesti TEDDY-tutkimusprotokollan mukaisesti. Tietojen käsittelyssä käytetään ainoastaan koodinimiä, joista yksittäisen lapsen henkilöllisyys ei käy selville.

- Milloin minun pitäisi palauttaa aktiviteettimittari ja valmis toimintapäiväkirja?

Postita mittari (ja kolmen päivän ruokapäiväkirja saamassasi palautuskirjekuoressa) TEDDY-henkilökunnalle mahdollisimman pian mittausjakson päätyttyä.

Kiitos, että olette mukana TEDDY-liikuntatutkimuksessa!

TEDDY-Messgerät für körperliche Aktivität - Fragen und Antworten

Die folgenden Informationen sollen bei der Erfassung der Daten zur körperlichen Aktivität helfen.

**Sollten Sie Fragen haben, können Sie jederzeit das TEDDY-Team unter 0800-3383339 anrufen.

Bemühen Sie sich bitte, das Messgerät nicht zu verlieren oder zu beschädigen. Sollte es jedoch verloren gehen oder beschädigt werden, rufen Sie bitte sofort das TEDDY-Team an. Der Ersatz oder notwendige Reparaturen sind für Sie kostenlos. **Funktionsuntüchtige Messgeräte müssen jedoch zurückgegeben werden. In diesem Fall schicken wir Ihrem Kind ein neues Messgerät und planen die 7-tägige Aktivitätsaufnahme neu.

**Sollte das Gerät versehentlich nass oder beschädigt werden oder verloren gehen, rufen Sie bitte das TEDDY-Team an: 0800-3383339

- Was ist ein Aktivitätsmessgerät?

Das Aktivitätsmessgerät ist ein kleines, leichtes Messgerät, das an einem Gürtel um die Taille getragen wird. Es misst die körperliche Aktivität, indem es alle Bewegungen Ihres Kinds aufzeichnet.

Das Gerät wird nicht von magnetischen Materialien beeinflusst.Es gibt keine Töne oder andere Signale ab. Ihr Kind kann das Gerät beim Passieren von Sicherheitskontrollen, z.B. auf Flughäfen, tragen; es wird KEIN Alarm ausgelöst.

Das Gerät ist nicht wasserdicht. Der schwarze Gummiverschluss auf der Vorderseite des Geräts soll verhindern, dass Flüssigkeiten in das Gerät dringen. **Bitte achten Sie darauf, dass das schwarze Gummiband fixiert bleibt und öffnen Sie es nicht.**

Auf der Rückseite des Aktivitätsmessgeräts Ihres Kinds befindet sich eine Nummer. Diese Nummer steht auch auf dem Aktivitätsprotokoll Ihres Kinds. Bitte lassen Sie den Aufkleber auf dem Messgerät.

- Wie wird das Aktivitätsmessgerät getragen?

Das Messgerät wird über der rechten Hüfte getragen. Um korrekte Daten erfassen zu können, muss das Gerät eng anliegen und darf nicht „schlackern“. Für eine korrekte Messung darf Ihr Kind das Gerät nicht auf dicken Kleidungsstücken wie Pullovern oder Mänteln tragen. Es spielt keine Rolle, welche Seite des Geräts nach oben zeigt.

- Muss mein Kind das Aktivitätsmessgerät immer tragen?

Ihr Kind soll das Gerät während der gesamten 7 Tage tragen. Vor Wasseraktivitäten wie Baden/Duschen, Schwimmen und in Wasserparks muss das Messgerät jedoch abgenommen werden. Das Gerät sollte auch nicht im Regen nass werden. Das Messgerät ist stabil, Sie müssen sich also keine Sorgen machen, dass es bei den normalen Aktivitäten Ihres Kindes beschädigt werden könnte. Dazu gehören auch Sportarten mit Körperkontakt (Fußball, Rugby usw.). Für uns ist es wichtig, die Aktivität Ihres Kinds während dieser Zeiten zu messen. Durch das Tragen des Geräts während solcher Aktivitäten entsteht für Ihr Kind und andere Kinder keine Verletzungsgefahr. Sollten Sie diesbezüglich Bedenken haben, können Sie Ihr Kind jedoch bitten, das Gerät bei Sportarten mit Körperkontakt abzunehmen.

- Wann soll mein Kind mit dem Tragen des Geräts beginnen?

Bitte weisen Sie Ihr Kind an, das Messgerät am ersten Tag Ihres Protokolls direkt nach dem Aufwachen anzulegen. Das Messgerät aktiviert sich von selbst. Am 8. Tag kann Ihr Kind das Messgerät nach dem Aufwachen abnehmen. Auf diese Weise wird gewährleistet, dass wir ausreichend Daten für die Analyse des Aktivitätsgrads Ihres Kinds erfassen können. Bitte halten Sie den Plan auf dem Aktivitätsprotokoll so genau wie möglich ein.

- Was geschieht, wenn mein Kind in der Schule ist?

Das Gerät soll auch in der Schule getragen werden. Wir stellen ein Schreiben bereit, das den Lehrern erklärt, warum Ihr Kind das Gerät trägt. Bitte füllen Sie die notwendigen Informationen in dem Schreiben aus. Wir verstehen, dass Sie nicht immer wissen können, ob Ihr Kind das Messgerät während der Schulzeit abgenommen hat. Es wäre jedoch hilfreich, wenn Sie Ihr Kind fragen könnten, ob es das Gerät in der Schule aus beliebigen Gründen abgelegt hat, und dies gegebenenfalls im Protokoll verzeichnen.

- Was bedeutet ein Blinken am Messgerät?

Im Gerät befinden sich eine grüne und eine rote LED. Sie zeigen einen möglichen technischen Fehler an. Bitte kontaktieren Sie TEDDY unter 0800-3383339! Die folgende Tabelle enthält weitere Erklärungen.

Kein grünes oder rotes Licht	Das Messgerät erfasst Daten.
Grünes Licht, dreimaliges Blinken	Die Batterie hat sich bei der Datenerfassung entladen. Es werden keine Daten erfasst. **Bitte rufen Sie sofort das TEDDY-Team an.**
Rotes Licht, zweimaliges Blinken	Die Batterie ist schwach. Es werden noch Daten erfasst.
Rotes Licht, dreimaliges Blinken	Die Batterie ist sehr schwach und wird bald ganz ausfallen. Tragen Sie das Messgerät weiter.

Bitte versuchen Sie nicht, das Gerät zu öffnen, um die Batterie zu prüfen oder auszutauschen.

- Was tue ich, wenn der schwarze Gummiverschluss abfällt und der USB-Anschluss offen liegt?

Die Abdeckung des USB-Anschlusses muss immer verschlossen bleiben. Während der Datenerfassung darf NICHT damit gespielt werden. Sollten Sie bemerken, dass die Abdeckung abgefallen ist, befestigen Sie bitte die Kappe, indem Sie sie mit der Kante einer Münze im Uhrzeigersinn zudrehen. (Ein flacher Schraubenzieher könnte den Kunststoff beschädigen.)

Wenn das schwarze Gummiband völlig kaputt geht, und die Kappe den USB-Anschluss nicht mehr abdecken kann, tragen Sie das Messgerät bitte weiterhin, achten Sie jedoch besonders darauf, dass kein Wasser in das Gerät eindringt. Ein Streifen Klebeband kann das Gerät schützen.

Teilen Sie dem TEDDY-Mitarbeiter bei der Rückgabe des Messgeräts mit, wenn der Verschluss beschädigt ist.

- Wozu dient das Protokoll?

Anhand des Protokolls können wir die Rohdaten besser analysieren, die wir vom Aktivitätsmessgerät erhalten. Bitte notieren Sie die Zeiten für Schlafen und für sportliche Aktivitäten wie z.B. Schwimmen bei denen das Gerät abgelegt wurde.

Wenn Ihr Kind das Aktivitätsmessgerät aus bestimmten Gründen, z.B. wegen Teilnahme an Wettkampfsport und/oder sonstigen geregelten Aktivitäten (siehe folgende Liste) abnimmt, bitten wir Sie die Gesamtzeit (in Minuten) pro Tag einzutragen. Falls das Aktivitätsmessgerät mehrmals an einem Tag abgenommen wurde, brauchen Sie die Dauer der Aktivitäten nicht einzeln aufzulisten. Aktivitäten die nicht im Folgenden aufgelistet sind, brauchen nicht protokolliert zu werden.

Sportunterricht; Leichtathletik, Ballspiele (jeder Art, z.B. American Football, Touch Football, Fußball, Basketball, Baseball, Tennis, Badminton, Hockey, Eishockey, Tischtennis, Handball, Floor Ball, Golf, Polo, Wasserball, Lacrosse etc.); Cheerleading; Turnen; Wrestling; Fechten; Eislaufen (inkl. Eiskunstlauf und Eisschnelllauf); Wintersportarten (alles außer Ski-Abfahrt und Snowboardfahren); Rollerblading; Tanzen; Kampfsport; Surfen; Klettern (in der Halle oder im Freien); Reiten (auch Rennreiten)

Geben Sie bitte auch an, ob der Aktivitätsgrad typisch, höher oder niedriger ist, während Ihr Kind das Messgerät trägt.

- Was geschieht mit den Informationen, die vom Aktivitätsmessgerät und im Protokoll erfasst werden?

Die TEDDY-Studie behandelt die Informationen, die von dem Messgerät erfasst werden, gemäß dem TEDDY-Prüfplan streng vertraulich. Die Informationen, die Sie bereitstellen, werden nur zwischen Prüfärzten ausgetauscht und nur anonym freigegeben.

- Wann muss ich das Aktivitätsmessgerät und das ausgefüllte Protokoll zurückgeben?

Bitte schicken Sie das Gerät und das Protokoll zeitnah zurück an das TEDDY-Team.

Medidor de actividad física de TEDDY: Preguntas y Respuestas

A continuación aparece más información para ayudarlo con la obtención de datos de actividad física.

**Si en cualquier momento tiene preguntas, llame al centro de TEDDY al: (número local)

Trate de no perder o dañar el medidor. Sin embargo, si lo pierde o se daña, llame al personal de TEDDY inmediatamente. No se le cobrará el reemplazo ni la reparación. **Aun así, necesitamos que devuelva el medidor, incluso si está descompuesto. Si esto sucede, le enviaremos a su hijo otro medidor de actividad y reprogramaremos el monitoreo de actividad de 7 días.

**Si el medidor se moja, se daña o se pierde accidentalmente, llame al estudio TEDDY al: (número local)

- ¿Qué es el actígrafo?

El medidor de actividad es un monitor pequeño y ligero que se pone alrededor de la cintura en un cinturón. Mide la actividad física al registrar todos los movimientos de su hijo.

Este medidor NO CONTIENE PLOMO. No emitirá ninguna señal inalámbrica ni sonido. Los materiales magnéticos no lo afectarán. Su uso NO interferirá con el paso de su hijo a través de los controles de seguridad, como los que hay en el aeropuerto.

Este medidor no es a prueba de agua. La cinta negra de hule al frente del medidor tiene la finalidad de impedir que los líquidos entren al monitor. **Asegúrese de que la cinta negra de hule se mantenga en su lugar todo el tiempo y no juegue con ella.**

Al reverso del medidor de actividad de su hijo aparece un número. Este será el mismo número que se encuentra en el registro de actividades de su hijo. Deje la etiqueta en el medidor.

- ¿Cómo ponerse el medidor de actividad?

Póngase el medidor sobre el lado derecho de la cadera. Para contribuir a una obtención de datos útiles, el medidor no debe estar volteándose, sino que debe quedar bien. No haga que su hijo se ponga el medidor por encima de ropa gruesa, como suéteres o abrigos. No importa qué lado del medidor esté hacia arriba.

- ¿Mi hijo deberá ponerse el medidor de actividad todo el tiempo?

Haga que su hijo use el medidor durante los 7 días completos. Sin embargo, quite el medidor para actividades con agua, como bañarse, nadar y visitar parques acuáticos. Además, intente que el medidor no se moje de agua de lluvia. El medidor es resistente, así que no se preocupe de que se dañe durante las actividades habituales de su hijo, incluso si incluyen cosas como deportes de contacto (futbol, *rugby*, etc.) Es importante para nosotros el medir la actividad de su hijo en esos momentos. Usar el medidor durante actividades como estas no dañará a su hijo ni a otros niños. Sin embargo, si esto le preocupa, está bien pedirle a su hijo que se quite el medidor durante deportes de contacto.

- ¿Cuándo debe comenzar mi hijo a usar el medidor?

Haga que su hijo se ponga el medidor justo después de que se despierte el primer día de su registro. El medidor comenzará a funcionar por sí solo. En el día 8, su hijo deberá quitarse el medidor cuando despierte. Esto ayudará a garantizar que tengamos suficientes datos para analizar el nivel de actividad del niño. Siga el programa de uso que aparece al frente del registro de actividades lo más posible.

- ¿Qué sucederá cuando mi hijo esté en la escuela?

Anime a su hijo a usarlo en la escuela. Le entregaremos una carta en la que se explica a los maestros por qué su hijo está usando el medidor. Usted debe llenar los detalles pertinentes de la carta. Entendemos que quizás no siempre sepa si su hijo se quitó el medidor de actividad durante las horas de escuela. Sería útil si pudiera preguntarle a su hijo si se quitó el medidor en la escuela por algún motivo y anotarlo en el registro.

- ¿Para qué sirven las luces del medidor?

El medidor tiene un LED verde y un LED rojo que parpadean en diferentes patrones para indicar los niveles de batería. La luz roja no parpadeara antes o durante la colección de información. La luz roja parpadeara cuando ocurran errores técnicos. Véase la tabla de abajo. Y comuníquese con el personal de TEDDY si la luz roja parpadea.

Ni la luz verde ni la luz roja están encendidas.	El medidor está reuniendo datos.
La luz roja está encendida y parpadea 2 veces.	La batería está baja. Aún se están obteniendo datos.
La luz roja está encendida y parpadea 3 veces.	El nivel de la batería está muy bajo y está por agotarse. Siga usando el medidor.

No intente abrir el medidor para revisar el nivel de la batería o cambiarla.

- ¿Qué pasa si la cinta negra de hule se cae del medidor y el puerto USB queda expuesto?

La cubierta del puerto USB debe permanecer colocada en todo momento. NO juegue con ella durante la obtención de datos. Si nota que la cubierta se ha caído, use el borde de una moneda para fijar la tapa girándola en el sentido de las manecillas del reloj. (Un desatornillador de cabeza plana puede romper el plástico).

Si la cinta negra de hule se rompe completamente y la tapa ya no cubre el puerto USB, siga usando el monitor y sea extremadamente cuidadoso para evitar que le entre agua. Un pedazo de cinta adhesiva en la abertura ayudará a evitar que entre agua al medidor.

Notifique al personal de TEDDY de la cinta rota cuando devuelva el monitor.

- ¿Para qué sirve el registro?

El registro nos ayuda a analizar mejor los datos sin procesar que obtenemos del medidor de actividad. Le pedimos que registre el tiempo que pasa durmiendo y cuando el monitor es removido debido a actividades acuáticas (tal como natación) o alguna otra actividad deportiva.

Si su niño removió el monitor mientras participaba en las actividades siguientes, por favor escriba la duración total (en minutos) por día. No necesita especificar la duración de cada actividad, si hay más de una actividad en el mismo día. No necesita anotar una actividad si no esta listada.

Clase de educación física; Atletismo; Juegos de pelota (cualquier deporte con pelota, como fútbol americano, fútbol americano de toques, fútbol, básquetbol, béisbol, softball, tenis, badminton, hockey sobre hierba, hockey sobre hielo, tenis de mesa (ping-pong), balonmano, “floor ball”, golf, polo, waterpolo, lacrosse, etc); Animación (cheerleading); Gimnasia; Lucha libre; Esgrima; Patinaje (incluyendo patinaje sobre hielo y “short track”); Otros deportes de nieve aparte de esquí de descenso y “snowboarding”; Patinaje con patines de ruedas en línea; Baile; Artes marciales; Surfing; Escalada (en roca artificial o en montaña); Montar a caballo (incluyendo como jockey).

También nos gustaría que indicara si el nivel de actividad es el habitual, es mayor o menor cuando su hijo usa el medidor de actividad.

- ¿Qué sucederá con la información reunida en el medidor de actividad y el registro?

El estudio TEDDY tratará la información reunida por el medidor con estricta confidencialidad, de acuerdo con el protocolo del estudio TEDDY. La información que entregue se compartirá únicamente con los investigadores del estudio y no se entregará de ninguna manera que permita que se lo identifique.

- ¿Cuando debo devolver el medidor de actividad y registro completado?

Tráigalos a su próxima cita de TEDDY junto con su registro de dieta de 3 días. Es muy importante que devuelva el monitor después de los 7 días de haberse usado.

FAQ TEDDY aktivitetsmätare

Här kommer ytterligare upplysningar som kan vara till hjälp vid insamlingen av data gällande fysisk aktivitet.

- Närhelst du har frågor, var god ring din TEDDY-sköterska
- Om du tappar bort eller skadar Actigrafen, ring din TEDDY-sköterska omgående.
  Om detta skulle inträffa, kommer vi att skicka en ny Actigraf till ditt barn och lägga ett nytt sju dagars schema för aktivitetsmätningen. Vi kommer inte att kräva att du ersätter eller reparerar Actigrafen. **Vi behöver ändå få tillbaka mätaren, även om den är trasig.**

- Vad är en Actigraf?

Actigrafen är en apparat som mäter fysisk aktivitet genom att registrera barnets rörelser och dess intensitet.

Actigrafen är inte vattentät. Den svarta gummistroppen på dosans framsida är till för att hindra vätska från att tränga in i apparaten. **Var god se till att den svarta gummistroppen är på plats hela tiden och lek inte med den.**

På baksidan av barnets Actigraf finns ett nummer. Detta är samma nummer som på barnets aktivitetslogg. Låt klistermärket sitta kvar på dosan.

- Hur bärs Actigrafen?

Bär Actigrafen ovanför den högra höften. För att kunna hjälpa till att samla in data med bra kvalitet så ska dosan sitta nära kroppen. Om barnet vill, låt då barnet bära Actigrafen utanpå en tunn T-shirt. Låt inte barnet bära Actigrafen utanpå tjock klädsel såsom en tröja eller jacka. Det spelar ingen roll vilken sida av Actigrafen som är vänd uppåt.

- Ska barnet bära Actigrafen hela tiden?

Låt barnet bära Actigrafen i sju hela dagar. Ta av Actigrafen vid vattenaktiviteter såsom bad, simning och lek i vattenparker. Försök också att hålla den torr vid regn. Mätaren är hållbar, så oroa dig inte för att den ska skadas under barnets vanliga aktiviteter, även om dessa inbegriper sådant som kontaktsporter (fotboll, rugby etc.). Det är viktigt för oss att mäta barnets aktivitet vid dessa tillfällen.

- När ska barnet börja bära Actigrafen?

Låt barnet sätta på sig Actigrafen direkt efter uppvaknandet på morgonen av mätperiodens första dag. Mätaren startar av sig själv. På den åttonde dagen ska barnet ta av mätaren då det vaknar. Detta bidrar till att säkerställa att vi har tillräckligt med data för att kunna analysera barnets aktivitetsnivå. Var god följ schemat som återfinns på framsidan av aktivitetsloggen så noga som möjligt.

- Hur blir det då barnet är i skolan?

Uppmuntra barnet att bära den i skolan. Vi tillhandahåller ett brev som förklarar för lärarna varför barnet bär mätaren. Du ska fylla i de relevanta uppgifterna i brevet. Vi förstår att du kanske inte alltid vet om ditt barn har tagit av Actigrafen under skoltimmarna. Det skulle vara till hjälp om du kunde fråga ditt barn om han/hon har tagit av Actigrafen i skolan av någon anledning och föra in detta i loggen.

- Vad händer om den svarta gummistroppen faller av mätaren och USB-porten blottläggs?

Skyddet till USB-porten ska vara kvar hela tiden. Lek inte med detta under datainsamling. Om du märker att skyddet har fallit av, lås huven genom att vrida den medurs med hjälp av kanten på ett mynt. (En platt skruvmejsel kan bräcka plasten.)

Om den svarta gummistroppen går helt sönder och huven inte längre kan täcka USB-porten, fortsätt att bära Actigrafen, men var ytterst noggrann med att inte låta vatten komma in i apparaten. En bit tejp över öppningen hjälper till att stänga ute vatten från Actigrafen.

Underrätta din TEDDY-sköterska om den trasiga stroppen då Actigrafen återlämnas.

- Vad är Actigrafens lampor till för?

Det finns en grön och en röd LED-lampa på dosan. Den gröna lampan kommer inte att blinka innan eller under datainsamlingen. Den röda lampan kommer att lysa om det uppstår något fel på mätaren. Se tabellen nedan. Kontakta din TEDDY sjuksköterska om den röda lampan lyser under datainsamlingen.

Inget grönt eller rött ljus	Actigrafen samlar in data.
Röda ljuset på, två blinkningar åt gången	Batterinivån är låg. Data samlas fortfarande in.
Röda ljuset på, tre blinkningar åt gången	Batteriet är lågt och på väg att dö. Behåll mätaren på.

Försök inte öppna Actigrafen för att kontrollera batterinivån eller byta ut batteriet.

- Vad är loggen till för?

Loggen hjälper oss att bättre analysera de rådata som vi får från Actigrafen. Vi ber dig att föra in den tid som mätaren använts under sömn och när mätaren inte använts under vattenaktiviteter(simning) och andra sportaktiviteter.

Om ditt barn tog av sig Actigrafen inför när han/hon skulle delta i följande sportaktiviteter, skriv då ned den totala tiden (antal minuter) idrottsaktivitet på en dag. Du behöver inte ange tidsperioden för varje aktivitet om det var flera än en.

Du skall registrera aktiviteter som är listade nedan:

Idrott i skolan, friidrott, bollsporter (t.ex. fotboll, handboll, tennis, badminton, volleyboll, innebandy, bordtennis, ishockey, basket, rugby); gymnastik, cheerleading, dans, brottning, kampsport, fäktning, ridning, rullskridskoåkning, konståkning,

- Vad kommer att hända med de uppgifter som samlas in på Actigrafen och i loggen?

TEDDY-studien behandlar de uppgifter som samlas in med hjälp av Actigrafen konfidentiellt i enlighet med TEDDY-studiens rutiner. De uppgifter du lämnar kommer endast undersökningens forskare till del och kommer inte att offentliggöras på något sätt som gör det möjligt att identifiera ditt barn.

När ska jag återlämna Actigrafen och den ifyllda loggen?

Det är mycket viktigt att mätaren återlämnas snarast efter 7 dagars mätning.

Appendix 19D. Meter Letter for Teacher

Physical Activity Assessment

Letter for School Teachers

Dear _____:

My child, _____,

is taking part in a research study that evaluates factors that may affect children's health.

The study includes collecting physical activity data over a period of 7 days using an activity monitor. The monitor is a small, lightweight device that is worn around the waist.

I would like to let you know that my child is wearing the monitor for 7 consecutive days for this project. It is important that the monitor is worn at all times and only by my child, except during an activity involving water. The monitor is sturdy and can be worn during activities like contact sports (e.g. soccer, rugby). It will not emit any sound or wireless signal. If the monitor is removed due to either potential water exposure or school policy, please remind my child to put the monitor back on as soon as possible.

Thank you for your assistance.

Name of Parent _____

Signature of Parent _____

Date _____

If you have any questions on this research project, please contact (name) at (clinic's phone #) or (clinic's email address).

Fyysisen aktiviteetin arviointi

Kirje koulun opettajille

Hyvä _____:

Lapseni _____

osallistuu tutkimukseen, jossa arvioidaan lapsen terveyteen mahdollisesti vaikuttavia tekijöitä.

Tutkimus sisältää fyysisten aktiviteettitietojen keräämisen 7 päivän ajalta aktiviteettimonitorin avulla. Monitori on pieni, kevyt laite, jota käytetään vyötärön ympärillä.

Haluan kertoa, että lapseni käyttää monitoria seitsemän peräkkäisen ajan kyseisen projektin ajan. On tärkeää, että monitori on kaikkina aikoina käytössä ja vain minun lapsellani lukuun ottamatta aktiviteetteja, joissa se altistuu vedelle. Monitori on lujarakenteiden ja se voi olla käytössä mm. sellaisten aktiviteetin aikana kuin kontaktiurheilu (mm. jalkapallo, amerikkalainen jalkapallo). Se ei lähetä mitään ääniä tai langattomia signaaleja. Jos monitori irrotetaan joko mahdollisen vedelle altistumisen tai koulun menettelytapojen vuoksi, muistuta lasta panemaan monitori takaisin mahdollisimman pian.

Kiitos avustasi.

Vanhemman nimi _____

Vanhemman allekirjoitus _____

Pvm _____

Jos sinulla on kysymyksiä tästä tutkimusprojektista, ota yhteyttä seuraavaan henkilöön: (nimi), (klinikan puhelinnumero #) tai (klinikan sähköpostiosoite).

Erfassung der körperlichen Aktivität

Brief an Lehrer

Sehr geehrte(r)_____!

Mein Kind, _____,

nimmt an einer Forschungsstudie teil, die verschiedene Gesundheitsfaktoren untersucht.

Zu dieser Studie gehört die Erfassung von Daten zur körperlichen Aktivität, die mittels eines Aktivitätsmessgeräts über einen Zeitraum von 7 Tagen erfolgt. Das Gerät ist klein und leicht und wird um die Taille getragen.

Bitte nehmen Sie zur Kenntnis, dass mein Kind das Gerät für dieses Projekt an 7 aufeinanderfolgenden Tagen tragen wird. Es ist wichtig, dass das Gerät immer und nur von meinem Kind getragen wird. Eine Ausnahme bilden Aktivitäten im oder mit Wasser. Das Gerät ist stabil und kann bei Aktivitäten mit Körperkontakt (z.B. Fußball, Handball) getragen werden. Es gibt keine Töne oder sonstige Signale ab. Sollte das Gerät wegen möglichem Wasserkontakt oder Schulvorschriften abgenommen werden, erinnern Sie mein Kind bitte daran, das Gerät so bald wie möglich wieder anzulegen.

Vielen Dank für Ihre Hilfe.

Name des Elternteils _____

Unterschrift des Elternteils _____

Datum _____

Sollten Sie Fragen zu diesem Forschungsprojekt haben, wenden Sie sich bitte an das Studienteam unter der kostenlosen Hotline 0800-3383339 .

Evaluación de actividad física

Carta para los maestros de la escuela

Estimado _____:

Mi hijo, _____,

participa en un estudio de investigación para evaluar los factores que pueden afectar a la salud de los niños.

El estudio implica reunir datos de la actividad física durante un período de 7 días mediante el uso de un monitor de actividad. El monitor es un dispositivo pequeño y ligero que se pone alrededor de la cintura.

Me gustaría informarle que mi hijo usará el monitor durante 7 días consecutivos para este proyecto. Es importante que sólo mi hijo use el monitor y que lo use todo el tiempo, excepto durante cualquier actividad que implique contacto con agua. El monitor es resistente y puede usarse durante actividades como deportes de contacto (por ejemplo, futbol o *rugby*). No emitirá ningún sonido ni señal inalámbrica. Si mi hijo debe quitarse el monitor debido a posible exposición al agua o a políticas escolares, por favor recuérdele que se lo vuelva a poner lo antes posible.

Gracias por su ayuda.

Nombre del padre o de la madre _____

Firma del padre o de la madre _____

Fecha _____

Si tiene alguna pregunta sobre este proyecto de investigación, comuníquese con (nombre) al (n.° de teléfono de la clínica) o en (correo electrónico de la clínica).

Mätning av Fysisk Aktivitet

Brev till skolan

Till: _____

Mitt barn, _____,

deltar i en undersökning som utvärderar faktorer som kan inverka på barns hälsa.

Undersökningen inbegriper insamlande av uppgifter om fysisk aktivitet över en sjudagarsperiod genom användande av en så kallad Actigraf. Actigrafen är en liten lätt apparat som bärs kring midjan.

Jag vill informera dig om att mitt barn bär Actigrafen under sju dagar i följd med anledning av detta projekt. Det är viktigt att Actigrafen bärs hela tiden och bara av mitt barn, utom i samband med vattenaktivitet. Actigrafen är robust och kan bäras under sådana aktiviteter som kontaktsporter (t.ex. fotboll, rugby). Den utsänder inga ljud eller trådlösa signaler. Om Actigrafen avlägsnas, på grund av antingen exponering mot vatten eller skolans policy, var vänlig att påminna mitt barn om att sätta på sig Actigrafen så snart som möjligt.

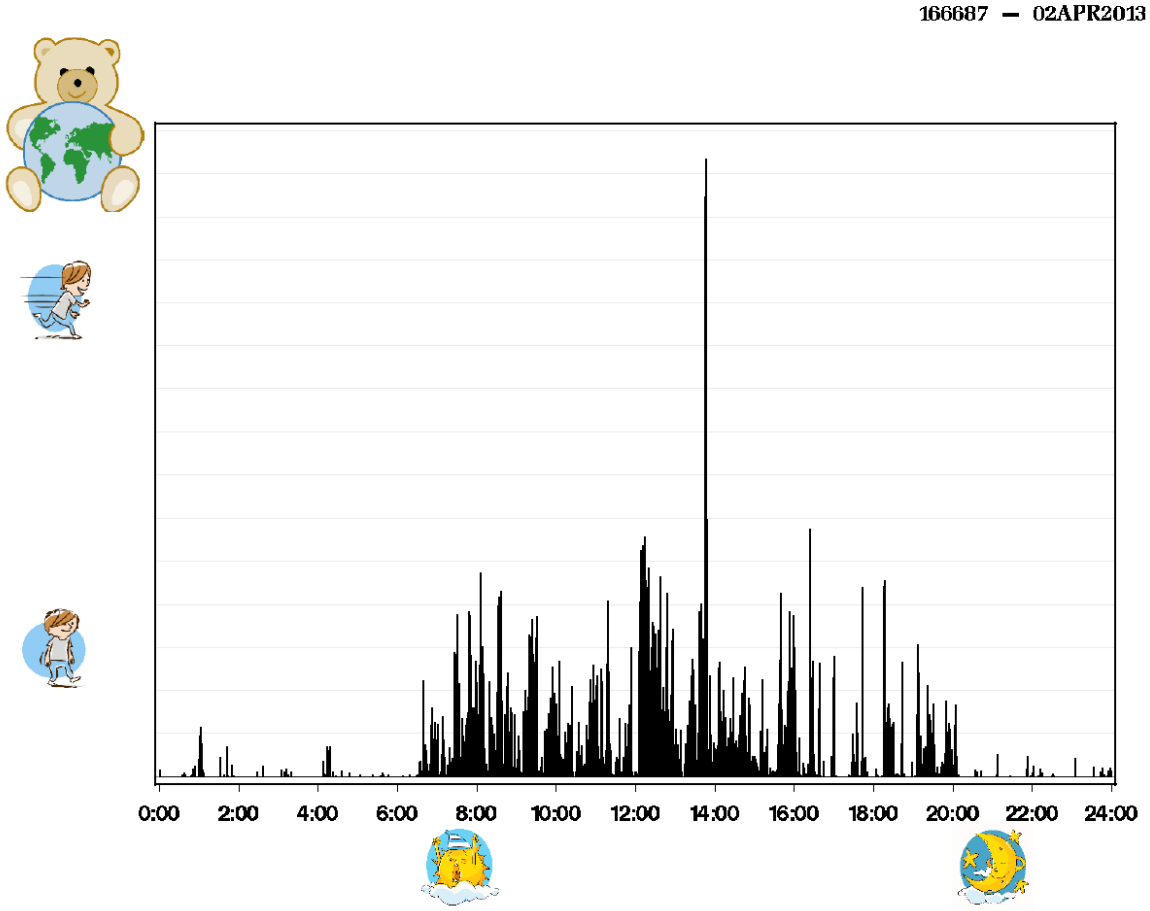
Tack för din medverkan.

Förälderns namn _____

Förälderns underskrift _____

Datum _____

Appendix 19E. Sample Activity Plot


166687 — 02APR2013
0:00
2:00
4:00
6:00
8:00
10:00
12:00
14:00
16:00
18:00
20:00
22:00
24:00

Appendix 19F: Activity Log Supplemental Page

*** PLEASE RECORD DATE AND TIME THE METER WAS REMOVED ON THE ORIGINAL ACTIVITY LOG ***

	Date dd/mmm/yyyy	Wake Up Time	Bedtime	Times meter not worn *during sport activities*		Times meter not worn *during sport activities*	Did child wear meter during sleep overnight?
				1	2	3	
Day 8		:	:	__:__ to __:__	__:__ to __:__	__:__ to __:__	Yes No Don't Know
Day 9		:	:	__:__ to __:__	__:__ to __:__	__:__ to __:__	Yes No Don't Know
Day 10		:	:	__:__ to __:__	__:__ to __:__	__:__ to __:__	Yes No Don't Know
Day 11		:	:	__:__ to __:__	__:__ to __:__	__:__ to __:__	Yes No Don't Know
Day 12		:	:	__:__ to __:__	__:__ to __:__	__:__ to __:__	Yes No Don't Know
Day 13		:	:	__:__ to __:__	__:__ to __:__	__:__ to __:__	Yes No Don't Know
Day 14		:	:	__:__ to __:__	__:__ to __:__	__:__ to __:__	Yes No Don't Know

Merkitse peruslomakkeeseen päivämäärä ja kellonaika jolloin mittari poistettiin

	Päiväys pp/kkk/vvvv	Heräämis aika	Nukkumaa nmenoaika	Kirjaa, jos mittari ei ole vyötäröllä pelien tai muun liikunnan aikana		Kirjaa, jos mittari ei ole vyötäröllä pelien tai muun liikunnan aikana	Pitikö lapsi mittaria yöunen aikana?
				1	2	3	
Päivä 8		:	:	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Kyllä Ei En tiedä
Päivä 9		:	:	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Kyllä Ei En tiedä
Päivä 10		:	:	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Kyllä Ei En tiedä
Päivä 11		:	:	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Kyllä Ei En tiedä
Päivä 12		:	:	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Kyllä Ei En tiedä
Päivä 13		:	:	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Kyllä Ei En tiedä
Päivä 14		:	:	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Pois vyötäröltä klo __ __: __ __ Vyötärölle klo __ __: __ __	Kyllä Ei En tiedä

***Bitte tragt das Datum und die Zeit, als das Gerät abgelgt wurde, auf dem originalen Aktivitätsprotkoll ein! ***

	Datum TT/MM/JJJJ	Aufstehzeit	Bettgehzeit	Zeiten Messgerät abgelegt bei körperlichen Aktivitäten (Schwimmen etc.)			Wurde das Messgerät über Nacht getragen?	Sonstiges
				1	2	3		
Tag 8		:	:	_ _: _ _ bis _ _: _ _	_ _: _ _ bis _ _: _ _	_ _: _ _ bis _ _: _ _	Ja Nein Unbekannt	
Tag 9		:	:	_ _: _ _ bis _ _: _ _	_ _: _ _ bis _ _: _ _	_ _: _ _ bis _ _: _ _	Ja Nein Unbekannt	
Tag 10		:	:	_ _: _ _ bis _ _: _ _	_ _: _ _ bis _ _: _ _	_ _: _ _ bis _ _: _ _	Ja Nein Unbekannt	
Tag 11		:	:	_ _: _ _ bis _ _: _ _	_ _: _ _ bis _ _: _ _	_ _: _ _ bis _ _: _ _	Ja Nein Unbekannt	
Tag 12		:	:	_ _: _ _ bis _ _: _ _	_ _: _ _ bis _ _: _ _	_ _: _ _ bis _ _: _ _	Ja Nein Unbekannt	
Tag 13		:	:	_ _: _ _ bis _ _: _ _	_ _: _ _ bis _ _: _ _	_ _: _ _ bis _ _: _ _	Ja Nein Unbekannt	
Tag 14		:	:	_ _: _ _ bis _ _: _ _	_ _: _ _ bis _ _: _ _	_ _: _ _ bis _ _: _ _	Ja Nein Unbekannt	

POR FAVOR ANOTE LA FECHA Y LA HORA DE QUITARSE EL MEDIDOR EN EL REGISTRO DE ACTIVIDADES ORIGINAL

	Fecha dd/mmm/aaaa	Hora de levantarse	Hora de acostarse	Tiempo que no se utilizó el monitor durante actividades deportivas 1	Tiempo que no se utilizó el monitor durante actividades deportivas 2	Tiempo que no se utilizó el monitor durante actividades deportivas 3	¿Utilizo su hijo/a el monitor durante la noche?
Día 8		:	:	__:__ to __:__	__:__ to __:__	__:__ to __:__	Sí No No se
Día 9		:	:	__:__ to __:__	__:__ to __:__	__:__ to __:__	Sí No No se
Día 10		:	:	__:__ to __:__	__:__ to __:__	__:__ to __:__	Sí No No se
Día 11		:	:	__:__ to __:__	__:__ to __:__	__:__ to __:__	Sí No No se
Día 12		:	:	__:__ to __:__	__:__ to __:__	__:__ to __:__	Sí No No se
Día 13		:	:	__:__ to __:__	__:__ to __:__	__:__ to __:__	Sí No No se
Día 14		:	:	__:__ to __:__	__:__ to __:__	__:__ to __:__	Sí No No se

GLÖM INTE ATT NOTERA DATUM OCH TID NÄR ACTIGRAFEN TOGS AV

	Datum år/månad/dag	Vaknade	Sängdags	Ifylls endast om Actigrafen inte bärs		Ifylls endast om Actigrafen inte bärs	Hade barnet mätaren på under natten?
				1	2	3	
Dag 8		:	:	__:__ till __:__	__:__ till __:__	__:__ till __:__	Ja Nej Vet inte
Dag 9		:	:	__:__ till __:__	__:__ till __:__	__:__ till __:__	Ja Nej Vet inte
Dag 10		:	:	__:__ till __:__	__:__ till __:__	__:__ till __:__	Ja Nej Vet inte
Dag 11		:	:	__:__ till __:__	__:__ till __:__	__:__ till __:__	Ja Nej Vet inte
Dag 12		:	:	__:__ till __:__	__:__ till __:__	__:__ till __:__	Ja Nej Vet inte
Dag 13		:	:	__:__ till __:__	__:__ till __:__	__:__ till __:__	Ja Nej Vet inte
Dag 14		:	:	__:__ till __:__	__:__ till __:__	__:__ till __:__	Ja Nej Vet inte

Appendix 19G. Activity Assessment Introduction Observation Form

TEDDY Staff: _____ Site: _____

Date of Observation: _____

In-person or Telephone (circle)

Set-up and Process	Satisfactory (S) Needs Improvement (NI) Not Applicable (NA)
1. ActiLife program set-up and ready-to-go	
2. Data collection package prepared	
3. Introduces himself/herself, establishes rapport	
4. Explains task	
5. Shows or references participant to key issues	
6. Demonstrates knowledge of completing the activity log	
7. Demonstrates knowledge of activity monitor	
8. Demonstrates ability to answer participants' questions about recording activities	
9. Uses notes to document change of data collection dates and/or family's mailing address	
10. Maintains a comfortable pace	
11. Thanks the participant	
12. Correctly initialize the monitor	
Comments or Concerns on Set-up and Introduction	

20. TEDDY Close-out Procedures

	BEFORE Last Visit	AT Last Visit	AFTER Last Visit
COL	- 13yrs: consent TEDDY Participant, reminder vaccine card, family DNA complete?, Request family members for next visit - 13.5: confirm receipt of vaccine card, family DNA complete?, review and update participant details page &TB summary, complete contact info, including 2 alternate contacts and PCP - 14yrs: confirm receipt of vaccination card, review/update family DNA - 14.5: complete review of family history q, review family DNA	- Final Q for parents and child - complete forms: PA, PE, DEF - Collect all samples - Review/update family DNA - Complete review of contact info - Review/organize blue chart: screening form, old HIPAA forms, Clinic cheatsheets, vaccine records, signatures/initials on consents/assents, - Hand out: results report, study findings, certificate, - Photo for the 15 year wall; study visit payment - AB+: discuss transition to DAISY for follow up	- Enter all data - Review/Update TEDDY child contact info and family preference for future contact - QC chart - Scan to TEDDY Scanned Docs - MH to contact family if any + results - Mail results letters
GEO	- 14.5 Visit: print out TB summary, reconcile/ correct items - Review any missing samples that we might collect at 15 year visit - Discuss accelerometer (AB+) at 14.5 or 14.75 -	- Conduct informed consent (if needed) - Complete forms (reimbursement, End of TEDDY questionnaire, celiac, TEDDY Book, pubertal assessment) - Hand out: results letter, pictograph, certificate, globe, volunteer letter, publication summary, symptoms card - Collect samples (regular 15 year visit + any missing catch-up samples)	- Review and correct errors - Special SOP for closing out participation record in local data base - ATL sends a final results note based on the 15 year results (unless it changes)
WAS	**Scheduling:** Review family DNA and schedule outstanding family members to be at visit Block 1.5 hours for 15 year visit when possible Encourage both parents to attend to hear final results **Clinical:** Look through the TEDDY summary. Be prepared to revisit all the currently open items (SD, AL, chronic, etc). (Only close items that came after a rejoin. Do not close out items from before a rejoin.)	**Part 1 – usual TEDDY visit** Complete interview, celiac sx, PE forms Collect toenails and water sample from family (they can always mail them in afterward) Make sure that the Last Questionnaire is completed or completed during the visit (ideally before) If applicable, consent for follow up in the Dew-it study. We will continue to offer quarterly/semi-annual follow up to all antibody positive subjects. (More info on Dew-it at end of document.	- Check chart: keep current contact sheet, visit notes, lab results, consent forms, vaccine records, fam DNA forms - contact info updates in database - Pull WAS state vaccine report, double check against both summaries - Fix all errors on summary - Track everything on DCC page

	Check DCC page for any pending blood samples: · HLA Sample Collection Form (9 m) · Non-HLA Genotyping Sample Collection Form (48 months) · 6 Year Whole Blood Storage SCF · Thyroid Confirm all materials for the visit – (materials will be prepared by usual bag-maker) TEDDY Folder to put everything in Certificate TEDDY summary of important findings Symptom cards (pictograph and 2-sided w/ contact info) Data collection tally (how many blood, nasal, etc) Final Result Report Volunteer hours letter (based on # of TEDDY visits age 7 and up) Repository consent and 6 ml no-gel SST in own blood bag Gift/money	Collect blood sample, nasal, urine, h/w *On all subjects (except LDP or those moving to Dew-it) request an additional 7mL red top and have Repository consent signed. We are asking for volunteers to give a small additional sample for in-house assay development. It is useful for us to have a wide range of positive and negative samples.* Confirm/ Update family contact information (use the contact info paper in chart). Request TEDDY kid email & phone **Part 2 – this is what we've done for you** Give and explain results letter Show symptoms cards **Part 3 – this is what you've done for us** Give the data collection tally Give volunteer hours letter and certificate Give the 'key findings so far' + ways to keep informed of future findings Give gift & visit payment	- Send out final results or call if any change - Check error report 30 days after AB negative: - After final follow-up change FU status in local data base to "study end" - Box up chart, hang file in bankers box (files will just be kept in the order they graduate, add local code to list on box, update excel sheet with box number and subject IDs AB positive that enroll in DEWIT: - Change follow-up status in local database to "Xfer DEWIT" - Subject will move to DEWIT sampling protocol for frequency and sample types - Chart, hanging file, clinician will stay the same as before

	BEFORE Last Visit	AT Last Visit	AFTER Last Visit
FIN	- After 14.5 visit: check open items in summary 1 & 2, compare that data open in summary 1 are ended in summary 2 (vitamins, day care activities…) - Ask school nurse for latest vaccine records if something is missing - Before 15 y visit: check report III.07 with tracking system - Prepare booklet for children (nurse's greetings, number of samples, staff picture), result letter, put together all materials (certificate, blanket)	- Families bring filled out last questionnaires, if not filled out yet, they will do during the visit - prepaid envelope for parent who is not attending the visit or if they do not bring water or toenail sample) - Discuss follow-up in DIPP study (AB+)	- save and verify all data - check error list - check paper files (remove sticky notes etc.) - remove informed consents - if change of AB status after the last blood drawn, study nurse will contact family
GER	- Review TB summary for open items - Check DCC page for open samples/ questionnaires - Put together folder& materials for last visit - Remind family to bring vaccination record to last visit - LDP: send all materials out in beforehand, make final call to discuss result letter, open questions	- Check open items from TB summary with family - Collect all open questionnaires/samples - Discuss final result letter - Make copy of vaccination record - Update contact information, get consent for further contact, tell family to contact TEDDY if child develops T1D - Talk about follow-up (AB+) - Hand out: globe, folder with booklet, result letter, volunteer letter, result letter, symptoms card	- Enter all data - Check error reporting system - Send out last autoantibody result letter (contact family if AB status changes)
SWE	- 14.5/ 14.75: ask family for special requests for last visit, give information about last visit, inform about end of TEDDY Q, inform AB+ about follow-up study - Before 15yrs visit: look through TB summary, review DCC page: open 9m, 48m or 6y whole blood sample? - Collection not done: use tracking - Prepare folder	- Normal TEDDY Visit - Collect end of TEDDY Q - Correct TB summary with family - Collect open 9m, 48m or 6y whole blood sample - Update family contact information - Hand out and explain folder, globe, star - Inform about webpage	- Go through file: remove drawings, personal letters, consent - Do all errors - Do corrections in TB summary - Tracking system DCC page - Control if all activity meters are uploaded correctly - Wait for last result and contact family

SUMMARY of TEDDY AFTER 15 FOLLOW-UP BY CENTER

As of 6/2022									Questior
US CENTERS		# Visits/YR GOAL		Autoantibodies	Blood Glucose	HbA1C	Height & Weight	Meds	Chronic & Acute Illness
TEDDY GRAD TRACK OF DAISY*	SAB	2		Y-4+ECL	Y	Y	Y	N	N
	MAB	4		Y-4+ECL	Y	Y	Y	W/CGM	W/CGM
FINLAND									
DIPP Follow-up	SAB	1		Y	Y	Y	Y	Y	Y
	MAB	1		Y	Y	Y	Y	Y	Y
GERMAY									
Only FDR-Local Study	SAB	1							
Local Study Only-Munich Bioresource**	MAB	Variable			Y	Y			
SWEDEN									
DIPIS+TEDDY Grad=ALUMNI	SAB	1		Y-4	Y	Y	Y	Y	Y
	MAB	4		Y-4	Y	Y	Y	Y	Y

*Used Parent Studies as Bridge until 11/2021: COL: DAISY; GA/FL: PAGOGA; WAS: DEW-IT
**If they don't enroll in local study recommend regular BG and HbA1C checks it their pediatrician
***FIN OGTT: OGTT In Tampere for MAB only; in Turku and Oulo for SAB and MAB
Allergies and diet data collected thoroughly in Oulo, Turku and Tampere collect some data
****Other Abbreviations
All=Allergies
SD=Special Diet

Section 20 – Appendix

A. Site Specific TEDDY Completion Certificates for Subjects

1. **COLORADO**
2. **FINLAND**
3. **GEORGIA/FLORIDA**
4. **GERMANY**
5. **SWEDEN**
6. **WASHINGTON**

B. Site Specific TEDDY Participation Summaries for Subjects

1. **GEORGIA/FLORIDA**
2. **SWEDEN**

C. Site Specific Volunteer Letter for College

1. **GEORGIA**
2. **FLORIDA**
3. **SWEDEN**

D. Site Specific Results Letter from 15 year visit

1. **SWEDEN**

E. Site Specific Information Letter for Inactive, Enrolled Subjects who do not show up to 15 year visit

1. **SWEDEN**

A1. Site Specific TEDDY Completion Certificate: Colorado

A2. Site Specific TEDDY Completion Certificate: Finland

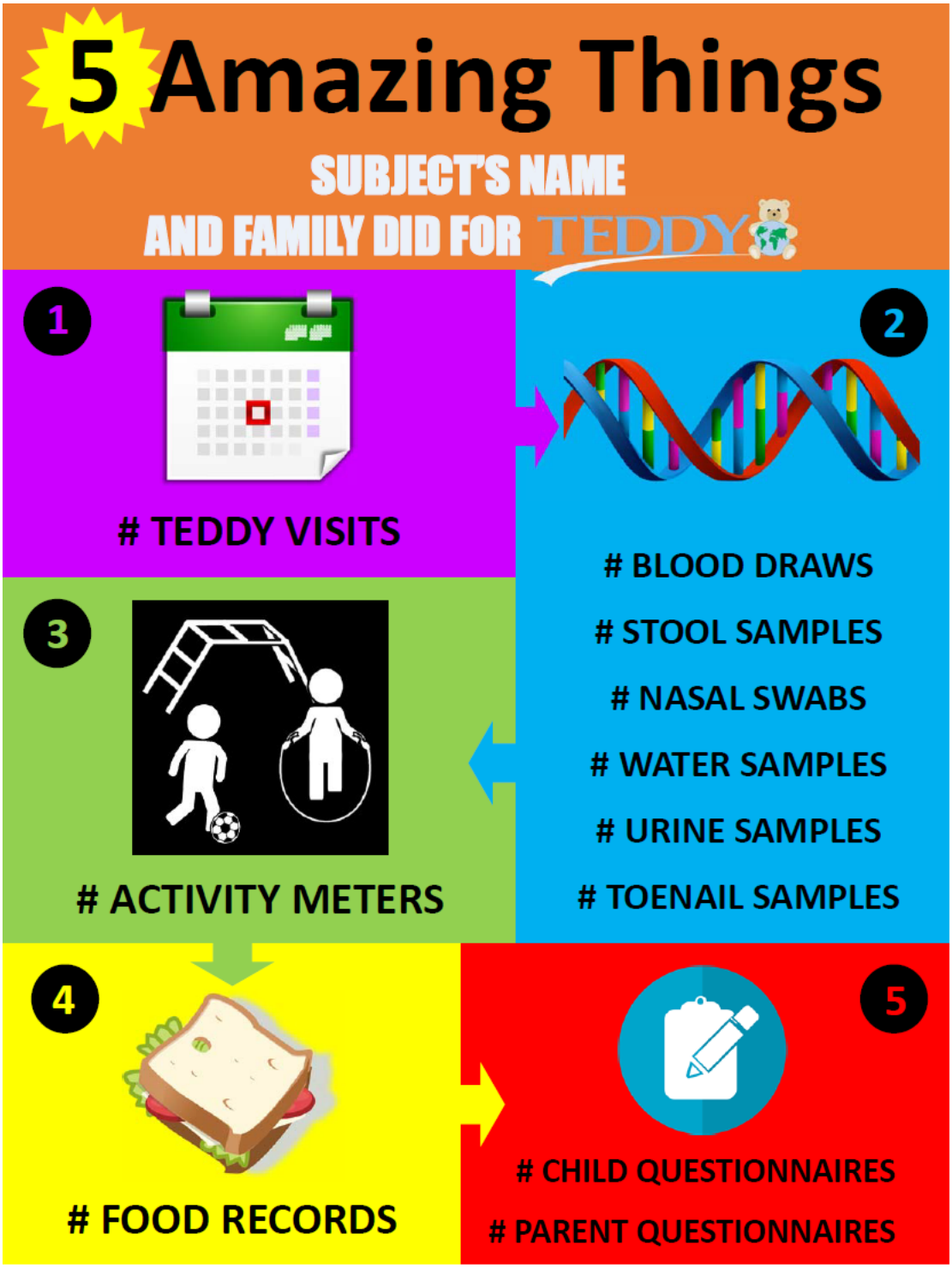
A3. Site Specific TEDDY Completion Certificate: Georgia/Florida

A4. Site Specific TEDDY Completion Certificate: Germany

A5. Site Specific TEDDY Completion Certificate: Sweden

A6. Site Specific TEDDY Completion Certificate: Washington

B1. Site Specific TEDDY Participation Summaries for Subjects: Georgia/Florida



B2. Site Specific TEDDY Participation Summaries for Subjects: Sweden

15 years in TEDDY

You have participated in the TEDDY study for 15 years. During these years you have contributed samples and information that researchers can use to find out why children develop autoimmune (type 1) diabetes, celiac, and thyroid disease.

During the 15 years in TEDDY you have collected:

Visits _____ 

Stool samples _____ 

Blood samples _____ 

Food records _____ 

Nasal swabs _____ 

Actigraph _____ 

Thank you for your contributions to research!

TEDDY
The Environmental Determinants of Diabetes in the Young

C1. Site Specific Volunteer Letter for College: Georgia

TEDDY Study
Center for Biotechnology and Genomic Medicine
Augusta University
1120 15th Street, CA-4123
Augusta, GA 30912-2400

Tel: 706-721-4161
Fax: 706-721-3688

Date

Dear (TEDDY participant name),

We wish to acknowledge and express gratitude for your years of service to The Environmental Determinants of Diabetes in the Young (TEDDY) Study, an international consortium study sponsored by the National Institutes of Health.

The rate of type 1 diabetes is increasing worldwide. During your time of service, TEDDY study findings have furthered our understanding of this increase. TEDDY scientists have also begun to uncover factors contributing to diabetes triggers and made steps towards developing a prevention or cure for this devastating condition. It is only through the service of volunteer participants like you that this will be accomplished.

We applaud that over the past 15 (or x) years, you have contributed X (1 hour per completed visit) hours of your time in selfless and voluntary participation in the TEDDY Study. Through this giving of your time and effort, you have demonstrated a sustained, long-term commitment to scientific inquiry as well as a concern for those impacted by type 1 diabetes that goes above and beyond the norm.

Many successes of young people are celebrated, such as academics and athletic achievements. The volunteering of your time as a research participant for a worthwhile and meaningful cause should also be considered among these accomplishments.

We celebrate you and your wonderful achievement.

Sincerely,

Jin-Xiong She, PhD
Director, Center for Biotechnology and Genomic Medicine
Augusta University

Diane Hopkins, MS, CCRC
TEDDY Study Manager

The TEDDY Study is funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Child Health and Human Development (NICHD), National Institute of Environmental Health Sciences (NIEHS), Juvenile Diabetes Research Foundation (JDRF), and Centers for Disease Control and Prevention (CDC).

C2. Site Specific Volunteer Letter for College: Florida

UF Diabetes Institute
College of Medicine
University of Florida
Gainesville, Fl. 32610-0296

Tel: 1-877-343-2377

Date:

Dear (TEDDY participant name),

We wish to acknowledge and express gratitude for your years of service to The Environmental Determinants of Diabetes in the Young (TEDDY) Study, an international consortium study sponsored by the National Institutes of Health.

The rate of type 1 diabetes is increasing worldwide. During your time of service, TEDDY study findings have furthered our understanding of this increase. TEDDY scientists have also begun to uncover factors contributing to diabetes triggers and made steps towards developing a prevention or cure for this devastating condition. It is only through the service of volunteer participants like you that this will be accomplished.

We applaud that over the past 15 (or x) years, you have contributed X (1 hour per completed visit) hours of your time in selfless and voluntary participation in the TEDDY Study. Through this giving of your time and effort, you have demonstrated a sustained, long-term commitment to scientific inquiry as well as a concern for those impacted by type 1 diabetes that goes above and beyond the norm.

Many successes of young people are celebrated, such as academics and athletic achievements. The volunteering of your time as a research participant for a worthwhile and meaningful cause should also be considered among these accomplishments.

We celebrate you and your wonderful achievement.

Sincerely,

Dr Deo

Desmond Schatz, M.D.
Professor and Associate Chairman of Pediatrics
Medical Director, UF Diabetes Institute
University of Florida

C3. Site Specific Volunteer Letter for College: Sweden

Dear _____,

We gratefully acknowledge your 15 years of service to The Environmental Determinants of Diabetes in the Young (TEDDY) study, which is sponsored by the National Institutes of Health. The rate of type 1 diabetes is increasing worldwide.

During your time of service, TEDDY scientists have begun to uncover factors contributing to the way the disease may be triggered. Unexpected findings are explored to accelerate research to explain the increasing rate in order to prevent or cure this devastating condition. It is only through the service of volunteer participants such as you that this will be accomplished.

We applaud that you during your first 15 years of life, have in 2-4 visits per year given blood and other samples, completed food diaries as well as numerous questionnaires. Through this selfless and voluntary participation in the TEDDY study, you have demonstrated a sustained, long-term commitment to scientific inquiry as well as a concern for those impacted by type 1 diabetes. Your contribution goes above and beyond the norm.

In addition, your participation has also made it possible for the TEDDY scientists to begin an inquiry into the way by which celiac disease may develop and be prevented.

Many accomplishments of young people are celebrated, such as academics and athletic achievements. The volunteering of your time as a research subject providing energy and resources for a worthwhile and meaningful cause should also be considered among such accomplishments.

We celebrate you and your wonderful achievement.

Sincerely,

The TEDDY Study Team

Professor
Åke Lernmark
Principal Investigator in Sweden

D1. Site Specific Results Letter from 15 year visit: Sweden

Till er som nu avslutat TEDDY studien

Vid ert sista besök blev ni lovade att få besked om de senaste provsvaren.

Eftersom vi inte kunnat nå er på telefon avslutas ert deltagande i TEDDY studien med detta brev.

[ ] Analyserna visar att det finns inga autoantikroppar för autoimmun (typ 1) diabetes och celiaki.

[ ] ----------

Om ni har frågor, vänligen kontakta er TEDDY sjuksköterska

Telefon:

Email:

E1. Site Specific Information Letter for Inactive, Enrolled Subjects who do not show up to 15 year visit: Sweden

The following letter is for inactive, enrolled Swedish subjects who did not show up to the 15 years visit. The letter informs them that the study is now ending, where to find information regarding symptoms and contact information for the Swedish site.

TEDDY

Till er som någon gång deltagit i TEDDY-studien.

Målet med TEDDY-studien är att ta reda på vilka faktorer i barnets omgivning som triggar immunsystemet att attackera bukspottskörtelns betaceller och hur sedan autoimmun (typ 1) diabetes utvecklas. Studien har varit igång sedan 2004 och av de 8667 deltagare som var med från början är nästan 70% kvar i studien.

Alla barn i TEDDY har en livslång förhöjd ärftlig risk för autoimmun diabetes.

TEDDY-studien följer barnen till 15 års ålder. Vi vill därför med detta brev avsluta vår kontakt och samtidigt tacka för ert deltagande och viktiga bidrag till forskningen.

Vad har TEDDY upptäckt?

Det kommer hela tiden nya upptäckter i TEDDY-studien. Läs om dessa på hemsidan: https://www.teddy.lu.se/. Prenumerera gärna där på TEDDYs nyheter.

Frågor om studien och vad TEDDY har kommit fram till besvaras gärna av professor Åke Lernmark. Tel: 040-39 19 01; Mejl: ake.lernmark@med.lu.se

Med vänliga hälsningar

Åke Lernmark
TEDDY- studien

Vi vill göra er uppmärksamma på diabetessymtom

ONORMAL TRÖTTHET | STORA URINMÄNGDER | ONORMAL TÖRST | AVMAGRING