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This Manual of Operations (MOO) should be used in conjunction with the TEDDY Study MOO sections referenced throughout this document.

1. Summary, Hypotheses and Specific Aims

1.1. Summary

Type 1 diabetes is associated with a pre-clinical period marked by the production of autoantibodies against insulin, GAD65, IA-2 and ZnT8. Prospective studies such as The Environmental Determinants of Diabetes in the Young (TEDDY) and TrialNet have used the production of these autoantibodies to identify children who are at a very high risk for the development of type 1 diabetes. We and others have shown that children diagnosed through studies that employ longitudinal monitoring of at-risk subjects have a lower hemoglobin A1c at onset, lower insulin dose through the first year of diabetes, and less hospitalization for diabetic ketoacidosis at onset than a similar group of children diagnosed in the community.

Preservation of C-peptide production has been shown to be associated with decreased complications such as retinopathy and microalbuminuria and decreased episodes of severe hypoglycemia. Hyperglycemia is toxic to the β-cell and prolonged hyperglycemia may lead to decreased C-peptide production. Through our previous analysis, we hypothesize that children diagnosed with diabetes through the TEDDY study are diagnosed at an earlier stage of type 1 diabetes (T1D) and that as such they will maintain the ability to produce C-peptide longer. We propose to analyze preservation of C-peptide over time in the children diagnosed with T1D through the TEDDY study and compare to a group of T1D controls from the community matched by age at diagnosis and by clinical center. In addition we propose to collect samples to investigate immunological changes that occur after diagnosis and whether these changes are related to the earlier diagnosis of T1D. We also plan to examine the extent to which earlier diagnosis leads to easier control as measured by continuous glucose monitoring. We also propose to analyze children diagnosed with T1D through TEDDY to compare the decline of C-peptide over time between the earlier and later stage of T1D diagnosis. Furthermore, we propose to analyze children diagnosed with T1D through TEDDY to compare the decline of C-peptide over time between the earlier and later stage of T1D diagnosis.

The children in the TEDDY cohort represent a unique resource in that they have been carefully followed and monitored for immunological (antibodies), metabolic (insulin and glucose) and gene expression changes prior to diabetes onset and through careful systematic follow-up after diagnosis. We propose to add to our understanding whether early diagnosis will improve their disease course after diagnosis. Our preliminary data suggests that prospective studies such as TEDDY, the DPT-1 and TrialNet do lead to a reduction in the incidence of diabetic ketoacidosis, but we do not know whether the benefit of close monitoring will lead to better outcomes beyond diagnosis. Should we establish this benefit, then it will lead to recommended changes in surveillance and monitoring of high risk pre-diabetes populations and perhaps a re-definition of the time point in the development of diabetes that exogenous insulin therapy is needed. The potential is to make a dramatic improvement in the lives of children diagnosed with type 1 diabetes.

1.2. Hypotheses

Hypotheses for TEDDY Cases and Community Controls:
We hypothesize that children diagnosed with type 1 diabetes through the TEDDY study are diagnosed earlier in the time course of diabetes. We hypothesize that they will have a higher level of C-peptide at diagnosis of type 1 diabetes compared with a control population of children diagnosed through the community. We hypothesize that this prolonged production of C-peptide will continue through the early years following diabetes diagnosis.

We also hypothesize that the prolonged production of C-peptide will result in better glycemic control, reduced levels of insulin dosages, fewer hypoglycemic and hyperglycemic episodes, but will be accompanied by a longer period of islet cell antibody production. We propose that earlier diagnosis of diabetes in children participating in the TEDDY study compared to community controls will predict better glycemic control and lower glycemic variability as assessed by continuous glucose monitoring (CGM) over the 3 year follow-up period.

Furthermore, we hypothesize that parents of children diagnosed through the TEDDY study will have higher levels of health-related quality of life and psychological functioning than community controls.

Secondary Hypotheses for TEDDY Cases:
We hypothesize that TEDDY children diagnosed earlier in the course of the disease (prior to diabetic ketoacidosis and symptoms) will maintain a higher level of insulin secretion than their TEDDY peers who were diagnosed later in the course of the disease. Among these subjects, we hypothesize that the C-peptide level at diagnosis will predict the rate of C-peptide loss and duration of C-peptide decline. We further predict that the level of C-peptide at diagnosis will affect the subject's ability to obtain optimal glucose control as measured by incidence and frequency of episodes of hyperglycemia, hypoglycemia, and HbA1c at desired levels. This will generate support for the conclusion that early intervention (diagnosis and treatment) lends to better short term metabolic outcomes.

We hypothesize that TEDDY children who are diagnosed earlier in the course of the disease will have better health-related quality of life and psychological functioning than those TEDDY cases diagnosed later in the course of the disease. We also predict that parents of TEDDY children diagnosed earlier will also have better health-related quality of life, psychological functioning, and less parenting stress.

1.3. Specific Aims

Aim 1: To evaluate subjects diagnosed with diabetes through the prospective TEDDY study and control children with type 1 diabetes of similar age for factors including C-peptide production at diagnosis, diabetic ketoacidosis, symptoms at diagnosis and HbA1c at diagnosis and to correlate these factors with decline and duration of decline of C-peptide loss.

Aim 2: To assess the impact of 'early' diagnosis on glucose control, quality of life and psychological functioning.

Aim 3: To collect and store samples for correlative studies to assess changes that occur before and after diagnosis of type 1 diabetes in TEDDY children with respect to T-cell and B-cell activity and gene expression as indicators of active autoimmunity.

2. Outcome Measures

2.1. Primary outcome measure

The primary outcome measure will be the level of C-peptide over time from diagnosis of diabetes.

2.2. Secondary outcome measures

Secondary outcome measures include presence of diabetic ketoacidosis at onset. C-peptide, islet cell antibodies, hemoglobin A1c and insulin dose throughout the study will be collected and analyzed. Glycemic control and glycemic variability will also be assessed through continuous glucose monitoring at predetermined study visits. Health-related quality of life and psychological functioning questionnaires will be administered to the children and their parents and compared between case and control groups. Specific constructs to be measured include diabetes-specific quality of life (child and parent), anxiety related to diabetes (child and parent), psychological well-being (parent), and pediatric parenting stress (parent). Among the TEDDY cases, we will also compare participants diagnosed earlier in the course of the disease (prior to diabetic ketoacidosis and symptoms) with TEDDY participants diagnosed later in the disease course.

Among the TEDDY children for whom samples have been obtained prior to and after diagnosis of type 1 diabetes, comparisons will be made of T-cell activity and gene expression prior to antibody development, post antibody development, post diagnosis of type 1 diabetes during which insulin secretory capability continues and after loss of C-peptide. As possible, stool samples will be collected to explore changes in the human biome for future studies focusing on changes in the biome that may predict C-peptide loss over time.

3. Potential Risks

Patients may feel brief pain at the time of the needle stick for the blood draw. In about 10% of cases, a small amount of bleeding under the skin will produce a bruise. The risk of temporary clotting of the vein is about 1% and the risk of infection of the bruise or significant external blood loss is less than 1 in 1,000.

The MMTT may result in transient hyperglycemia at end of study (BG>300 mg/dL). Subjects will be monitored for ketones and given insulin as prescribed by the investigator.

Continuous glucose monitoring (CGM) requires the insertion of a small plastic tube with a needle that is then removed. The small plastic tube stays in place for 5-7 days. There is a low risk of developing a local skin infection at the site of the sensor needle replacement. Itchiness, redness, bleeding and bruising at the insertion site may occur as well as local tape allergies.

4. Potential Benefits

While there may be direct benefit to subjects participating in this study due to more careful surveillance through study visits, the study is not designed to provide direct benefit to subjects participating in the study. There is the potential for indirect benefit if the studies reveal reasons for development or aggravation of islet autoimmunity. Early identification of these abnormalities may lead to prevention of disease or enhanced blood glucose control. Participation in DPT-1, DAISY, TEDDY and TrialNet has been shown to greatly reduce the severity of presentation and the risk of life-threatening diabetic ketoacidosis at the diagnosis of diabetes (10,11). Participants will be given their test results at the end of the study. This may be beneficial in assisting them and their health provider in diabetes management.

Participant enrollment may only begin with IRB approved consent forms. This is an observational study that meets the federal definition of minimal risk.

5. Study Oversight

The Study Chair has primary oversight responsibility of this protocol. Each site's Primary Investigator and their research team (co-Investigators, research nurses, clinical trial coordinators, and data managers) must be certified to conduct research in human subjects annually and are responsible for identifying adverse events. Aggregate report- detailed by severity, attribution (expected or unexpected), and relationship to the study protocol will be available from the Data Coordinating Center (DCC) at USF for site review. Adverse events will be reviewed once a month by the research team. A separate report detailing protocol compliance will also be available from the USF Data Coordinating Center for site review on a monthly basis. The research team will then evaluate whether the protocol or informed consent document requires revision based on these reports.

TEDDY investigators must comply with local institutional requirements regarding conflicts of interest and the need to inform subjects about any perceived conflicts should they have any.

6. Study Organization – Committees and Labs will be the same as TEDDY. Participating centers for this study include the University of Colorado, University of Turku, Lund University, Pacific Northwest Diabetes Research Institute (for case participants only) and the University of South Florida (DCC) – see TEDDY MOO section 2 for details.

7. Contact Information – will be the same as TEDDY – see TEDDY MOO section 3 for details.

8. Policies – will be the same as TEDDY – see TEDDY MOO section 4 for details.

9. Description of Population to be Enrolled

The study has a case-control design. Cases are children diagnosed with type 1 diabetes through the prospective TEDDY study and controls are patients diagnosed with type 1 diabetes from the community and followed at selected TEDDY centers. The TEDDY centers that will be participating in this study are Sweden, Finland and Denver, CO. The Pacific Northwest Diabetes Research Institute center in Seattle, WA will participate in this study, but currently only enrolls cases. If the Washington site is unable to enroll controls, then the Colorado site will be asked to enroll community controls to match the cases enrolled at the Seattle center. Participants will undergo visits with lab draws at regular intervals, i.e. at baseline, 3 months, 6 months, 12 months, 18 months, 24 months and every 6 months thereafter up until

60 months following their diagnosis of diabetes. For TEDDY participants, their post-diagnosis TEDDY visit will be used in lieu of the baseline visit for this study. Controls will be matched by age of diagnosis (plus or minus one year) and by their clinical center location (Washington controls may not be matched by clinical center).

Cases: Cases are children diagnosed with type 1 diabetes through the TEDDY study. They will be identified at onset of diabetes and referred by the TEDDY study coordinator to the study coordinator for the follow-up study.

Controls: Controls are children diagnosed with type 1 diabetes and treated at a TEDDY clinical center. Controls will be approached by their TEDDY treating physician for participating in this study and if interested will be invited to participate. Controls will be matched by age at diagnosis (plus or minus one year) and their clinical center location (Washington controls may not be matched by clinical center).

10. Subject Recruitment

Children diagnosed with type 1 diabetes through TEDDY will be followed by the primary care practitioner, depending upon the local type of health care system, for care of their diabetes. In addition, they will be informed of a follow-up study that is in place and referred to the study coordinator for the TEDDY follow-up study. We will make every attempt to enroll all patients diagnosed with type 1 diabetes through TEDDY in the follow-up study.

Children diagnosed with type 1 diabetes external to TEDDY and followed at a TEDDY clinical center will be informed of this study shortly after diagnosis of diabetes. They will be identified as eligible based on matching with the cases by age of diagnosis (plus or minus one year) and clinical center location (Washington controls may not be matched by clinical center). Participants who meet the inclusion criteria will be eligible for enrollment.

Table 1. Projected enrollment by site

T1D Cases	Cases Projected over the next 3 years	Controls Projected over the next three years	Total Projected Study Subjects over the next three years	Total Projected Study Subjects over the next three years (assuming approximately 75% enroll)
Denver	19	19 (possibly 16 others)	38 (possibly 54 others)	28 (possibly 40)
Finland	26	26	52	40
Sweden	34	34	68	52
Seattle	16	0 (possibly 16 others)	16 (possibly 32)	12 (possibly 24)
Total	95	95	190	144

10.1. Inclusion criteria

Inclusion criteria for TEDDY case subjects:

1. Participated in regular follow-up through the TEDDY study, i.e. seen within a year prior to diagnosis, and enrolled within 3 months of diagnosis.

2. Diabetes diagnosed:
    a. with symptoms of diabetes (e.g. polyuria, polydipsia) and confirmatory blood sugar greater than or equal to 200 mg/dL (11.1 mmol/L).
    b. fasting glucose greater than or equal to 126 mg/dL (7 mmol/L) and/or random blood sugar greater than or equal to 200 mg/dL (11.1 mmol/L) at least twice.
    c. abnormalities of oral glucose tolerance testing (OGTT) with fasting glucose greater than or equal to 126 mg/dL (7 mmol/L) and/or 2 hour post blood sugar greater than or equal to 200 mg/dL (11.1 mmol/L) at least twice.
    d. unequivocal hyperglycemia with acute metabolic decompensation (diabetic ketoacidosis).
3. Informed consent and assent of subjects where appropriate
4. Children greater than or equal to age 3 will be eligible.

Inclusion criteria for Control subjects:

1. Diabetes diagnosed:
    a. with symptoms of diabetes (e.g. polyuria, polydipsia) and confirmatory blood sugar greater than or equal to 200 mg/dL (11.1 mmol/L).
    b. fasting glucose greater than or equal to 126 mg/dL (7 mmol/L) and/or random blood sugar greater than or equal to 200 mg/dL (11.1 mmol/L) at least twice.
    c. abnormalities of oral glucose tolerance testing (OGTT) with fasting glucose greater than or equal to 126 mg/dL (7 mmol/L) and/or 2 hour post blood sugar greater than or equal to 200 mg/dL (11.1 mmol/L) at least twice.
    d. unequivocal hyperglycemia with acute metabolic decompensation (diabetic ketoacidosis).
2. Autoimmunity documented with positive GAD65, IA-2, ZnT8 and/or insulin autoantibodies within the first 3 months of diabetes onset.*
3. Matched to case subjects by age of diagnosis within one year and clinical center location.**
4. Followed and recruited in the clinic with informed consent and assent of subjects where appropriate.
5. Did not participate in any other prospective studies such as TrialNet, DAISY, TRIGR, etc.
6. Children greater than or equal to age 3 will be eligible.
7. Enrolled within 3 months of diagnosis.

*Autoantibody results from the samples collected at the first visit of this study will be used to determine if the control subject meets this inclusion criterion or not; the control subject will be allowed to enroll in the study and will be disenrolled should the first visit's autoantibody results be deemed negative. Sites may choose to "screen" the control subject through local autoantibody testing prior to enrolling the subject in the study. The local autoantibody results do not need to be submitted to the DCC.

**Washington controls may not be matched by clinical center

NOTE: If a control subject's first study visit autoantibody results are deemed negative, the site should be sure to complete a Change in Study Participation form for the subject by marking "5. Autoantibody results within 3 months of diabetes diagnosis deemed negative (for control subjects only)" under "Subject/family does not wish to participate further as of. . ." Since the subject will have been enrolled in the study for less than one

year, the site should replace the subject by enrolling a new control subject to match the case subject.

10.2. Exclusion criteria

1. Not diagnosed with diabetes
2. Do not provide informed consent
3. Children less than 3 years of age
4. The parent or primary caretaker refuses to have the child's samples stored at the Central Repository.
5. Subject has galactosemia

10.3. Duration of the study

The planned duration of the study is 5 years with recruitment during the first 3 years. The minimum duration of participation for each subject will be 2+ years, or until a subject's stimulated c-peptide is <0.05 ng/mL. The goal is to follow all subjects until loss of C-peptide production (identified by a <0.05 ng/mL stimulated c-peptide). HbA1c data will be collected at one year and two years after loss of c-peptide production. It is anticipated that at the end of the 5 year project, application will be made to continue the study. Some TEDDY children have already developed diabetes. We propose to enroll all such children who have developed diabetes within 3 months of the time this follow-up study begins (expected number 15). The TEDDY protocol provides for comprehensive data collection at diagnosis and up to 6 weeks post diagnosis. For these subjects the TEDDY post diagnosis visit will be used in lieu of the Follow-up Study baseline visit. Prospectively, if we allow recruitment to extend over three years, we would expect another 57 cases to be identified by TEDDY sites, bringing the total anticipated enrollment of cases to 72. We anticipate that 60 of these cases will be at centers participating in recruiting community controls, with the Denver site possibly enrolling 12 controls to match the Seattle center's cases. Thus, we aim to recruit 72 community controls matched by age at diagnosis (plus or minus one year) to the TEDDY cases. Allowing for a 15% dropout rate, we aim to retain 60 subjects in the TEDDY case group and will enroll 60 community controls.

10.4. Parent expresses interest in the Follow-up of Children Diagnosed with Diabetes 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 of Children Diagnosed with Diabetes study, but is presented in a conversational mode with time for questions and clarification.

Basic Elements of the Recruitment Conversation:

- Describe the basic aims of the study.
- Explain why it is important to study children with T1D.
- Explain what is involved in participating in the Follow-up of Children Diagnosed with Diabetes 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.
- 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. 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?"

10.4.1. Outcome: After hearing about the Follow-up of Children Diagnosed with Diabetes Study, parent wishes to enroll, scheduling first visit

The scripts below should be followed when a parent decides to participate in the study:

- Thank you, we really appreciate your help with the study. *For control subjects only:* I need to verify that the information that we have is correct.
  Child's Name
  Date of Birth
  Date of Type 1 Diabetes Diagnosis
  Address
  Phone Number
  Cell Phone Number
  Mom's Name
  Dad's Name

- If it would be okay, I would like to go ahead and schedule CHILD NAME's first visit, This visit should be within 3 months of diagnosis, which would be DATE. (SEE SCHEDULING SECTION). Because this is the first visit it will take a little longer than the usual 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. At the first visit we will explain all of the forms and the information we will ask from you in the future. We will also explain the consent forms to you and have you sign them.

- 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.

10.4.2. Outcome: After hearing about the Follow-up of Children Diagnosed with Diabetes Study, 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, to be sure to call the study within three months of diagnosis.
    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.
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. Welcome them to call if they have questions.
    b. Also try to obtain permission for the study team to call again to see where they are with this decision.

10.5. Parent isn't interested in hearing about the Follow-up of Children Diagnosed with Diabetes Study at this time

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.

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.

10.6. Obtaining Informed Consent (all clinical centers)

Upon identification, participants will be given a written consent form by qualified study personnel (the study coordinator and/or investigator or other designee). The personnel will understand the research study, will complete any necessary courses required by their Institutional Review Board/Ethical Review Board prior to implementing the consent process. The consent process will occur in a quiet setting, and the participant will be given time to review the written consent form and ask questions prior to the initiation of study procedures. The Informed Consent Form for this clinical study will be reviewed with patients (and their guardian in the case of children patients) prior to performing any study-related assessments. Asking the participant to explain the study in his/her own words will assess the patient's understanding and autonomy. Qualified personnel as listed above will then obtain written consent prior to the initiation of study procedures. The consent form requests consent for each time the individual has blood drawn for these studies. The participant will be given their signed copy of the written consent form (and assent forms where applicable). Model Informed Consent language is provided in Appendix A for clinical centers to tailor 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.

10.7. Assent procedure

An assent form has also been developed for participants as has been done for TEDDY. The assent process for each participant will be completed at an appropriate age as determined by the local IRB/Ethics board for each participating center. Those within that age range will be given the consent and assent forms requested and will have the opportunity to discuss the study apart from their parent(s) or guardian(s). This will allow these individuals to ask questions they might not have felt comfortable asking previously. In addition, the parent(s) or guardian(s) will be given the opportunity to discuss the study apart from the child or adolescent. Model Assent language is provided in Appendix B.

Authorization will be obtained during the Consent process by qualified personnel in the calm environment described above. The person obtaining authorization will explain the type of PHI that will be collected, how it will be stored and to whom it may be disclosed. If the patient agrees to authorize the use of their PHI for research, a signed and dated copy of the form will be provided to the subject.

10.8. HIPAA authorization (US Centers only)

Some US sites will require every participant agreeing to participation 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 site's local IRB.

10.9. Registration of subjects with the DCC

A Registration form should be completed for all TEDDY subjects who have developed Type 1 Diabetes within the time-frame to be eligible for the follow-up study, even if the subject will not participate in the Follow-up Study. The reason for this is so that the DCC can capture information on why the subject did not enroll in the Follow-up Study. A Registration form should be completed for all control subjects who are approached by the study staff.

10.9.1. Online Registration

1) Login to the TEDDY website, go to the "Protocols" section and click on "JDRF FOLLOW-UP"
2) Click on "Registration Form for Follow-up Study" under the Data Management heading on the left navigational bar.
3) Complete online Registration form.

4) Required fields to save the form include (these fields are marked with a red "*"):
    i. For cases:
        - Clinical Center
        - Visit Location Code
        - TEDDY Staff Code of interviewer
        - Was subject followed through the TEDDY Study or will he/she be enrolled as a community control?
        - Local Code (this is the same as the TEDDY Local Code)
        - Subject ID (this is the same as the TEDDY Subject ID)
    ii. For controls
        - Clinical Center
        - Visit Location Code
        - TEDDY Staff Code of interviewer
        - Was subject followed through the TEDDY Study or will he/she be enrolled as a community control?
        - Was this subject screened for TEDDY and found to be HLA ineligible?
            - If yes, enter the TEDDY local code and TEDDY subject ID
                - NOTE: a new local code and subject ID will be used in the JDRF follow-up study
        - Was this subject screened and found HLA eligible for TEDDY, but chose not to enroll?
            - If yes, enter the TEDDY local code and TEDDY subject ID
                - NOTE: a new local code and subject ID will be used in the JDRF follow-up study
        - Local Code (this is to be assigned by the Clinical Center just like in TEDDY)
        - Child's date of birth
        - Child's date of type 1 diabetes diagnosis
5) Once the form is complete click "Save", or "Save and Print" if you want a print out of the form.
6) Cases and controls will then be registered in the study and will have a status of "Registered"; cases will have a substatus of "Case" and controls will have a substatus of "Control". A unique Subject ID will be assigned to the control subjects by the DCC. This Subject ID number will appear on the Registration form underneath the child's date of type 1 diabetes diagnosis once the form is saved.

10.9.2. What to do if you submit a Registration Form for a subject by mistake

If you mistakenly register a subject (submit two registration forms for one subject, submit a registration 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"

10.10. Completion of Enrollment Form

Local centers will develop mechanisms for tracking the contacts made for recruitment into the Follow-up of Children Diagnosed with Diabetes study. The final status is recorded on the Enrollment Form on the study website which can be found on the specific subject's Participant's

Details Page. This form has fields to record the subject's study information, enrollment status, study history information, sex (controls only), birth number (controls only), race (controls only), ethnicity (controls only), mother's date of birth (controls only), father's date of birth (controls only) and family history of diabetes (controls only). The reason some of the data items are only collected from controls is because the data was already collected from the cases as part of the TEDDY Study. For subjects who enroll in the study, the date of contact is the date that the subject's parent(s) agreed to follow-up and signed the informed consent form. For subjects who refuse to be in the study, the date of contact is the date that the parent(s) indicated to the site that he/she does not want to participate in the study. If a subject agrees to follow-up and answers "Yes" to each of the inclusion criteria the subject's status will become "Enrolled" with a substatus of either "Case" or "Control". If a subject agrees to follow-up and answers "No" to one or more of the inclusion criteria the subject's status will become "Not Eligible" with a substatus of either "Case" or "Control". If a subject refuses to have his/her samples stored at the Repository the subject's status will become "Not Eligible" with a substatus of either "Case" or "Control". If prior to a control subject being enrolled in the Follow-up Study, the subject's autoantibody results within 3 months of diabetes diagnosis are deemed negative the study staff member should indicate this information under the "Exclusion Criteria" section of the Enrollment Form; once this exclusion criterion is selected the subject's status will become "Not Eligible" with a substatus of "Control" (NOTE: if a subject is deemed autoantibody negative within 3 months of diabetes diagnosis after being enrolled in the Follow-up Study this should instead be noted on the subject's Change in Study Participation Form). If a child is less than 3 years of age the study staff member should indicate this information under the "Exclusion Criteria" section of the Enrollment Form; once this exclusion criterion is selected the subject's status will become "Not Eligible" with a substatus of either "Case" or "Control". If a subject's first visit did not occur within 3 months of T1D diagnosis, the study staff member should indicate this information under the "Exclusion Criteria" section of the Enrollment Form and indicate the reason why; once this exclusion criterion is selected, the subject's status will become "Not Eligible" with a substatus of either "Case" or "Control". If a subject refuses to enroll the subject's status will become "Not Enrolled" with a substatus of either "Case" or "Control".

11. Administrative Procedures for Participant Scheduling – will be the same as TEDDY with a few minor changes to meet the details of the Follow-up of Children Diagnosed with Diabetes Study (such as when first visit can occur by, what to bring to visit, etc – see section 13 of this MOO for visit details for this study) - see TEDDY MOO section 8.1-8.3.4., 8.3.6.-8.3.8. and 8.4 (except no final questionnaire will be mailed and letter should not list the signs and symptoms of T1DM) for details

12. 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 TEDDY MOO section 8.3.5.1. for form instructions).
- 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 come back to the study. Note this response on the Change in Study Participation Form.

- Remind the family that they always have the opportunity to come back to the study if they wish. 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

NOTE: If the withdrawn subject is a control subject and has been enrolled in the study for less than one year, the site should replace the subject by enrolling a new control subject to match the case subject. We would NOT replace a control subject with a loss in c-peptide (stimulated c-peptide is <0.05 ng/mL) before one year of enrollment in the study; the subject would be considered as reaching the study endpoint and not withdrawn.

13. Study Procedures

13.1. Visits

Baseline visits for control participants will begin within 3 months of diagnosis of type 1 diabetes when metabolic control is generally attained. For cases the TEDDY post-diagnosis visit data will be utilized in lieu of the baseline visit. All subjects will then be followed at 3 months after diagnosis, 6 months, 12 months, 18 months, 24 months, 30 months and 36 months. If there remains C-peptide at the 36 month visit the subject will be followed every 6 months until the disappearance of C-peptide response (subjects will be followed until stimulated c-peptide is <0.05 ng/mL) or 60 months post-diagnosis.

NOTE: If a subject's stimulated c-peptide is <0.05 ng/mL, the site should be sure to complete a Change in Study Participation form for the subject by marking "7. Subject's stimulated c-peptide is <0.05 ng/mL" under "Subject/family does not wish to participate further as of. . ."

At baseline and each subsequent visit, blood draws for fasting and stimulated C-peptide (if possible to obtain stimulated c-peptide at baseline visit), antibody determination and PBMCs will be performed (see below). For control participants HLA typing will be conducted at the baseline visit to assess participants for the HLA DR, DQ genotypes. At the visit closest to onset of diabetes, an onset questionnaire will also be performed describing the clinical course at onset of diabetes; additional questionnaires regarding insulin dose, interval changes in history, including diabetes treatment, height, weight and HbA1c will be obtained at all visits. Quality of life and psychological questionnaires will be obtained at enrollment and at 3-month, 6-month, 12-month, 24-month, and 36-month visits. For subjects with C-peptide remaining, the Quality of Life and psychosocial questionnaires will also be collected at the 48 month and 60 month visits. If participants are unable to fully complete psychological questionnaires at the baseline visit due to time constraints, they may take these questionnaires home and mail back to the clinical center within 2 weeks.

NOTE: Should a subject refuse to complete the MMTT at the initial study visits (baseline and/or 3 month visit) it has been approved that the first MMTT can be completed at the 6 month visit, but as a study requirement the latest the first MMTT can be performed is at the 6 month visit.

A one-time stool sample may be collected from control subjects within 3 months of the diagnosis of type 1 diabetes (by the end of the 3 month visit window), if possible. Participants may opt not to participate in the stool sample collections. This will not affect the participant's ability to participate in the study.

Following the 3 month, 6 month, 12 month, 18 month, 24 month, 30 month, 36 month, 42 month, 48 month, 54 month and 60 month visits, participants will be asked to complete a 5-7 day period of continuous glucose monitoring (CGM) immediately following the visit with MMTT assessment of C-peptide, using continous glucose monitors (CGM), other CGMs or flash glucose monitors (FGM). Participants may opt not to participate in the continuous glucose monitoring. This will not affect the participant's ability to participate in the study.

Table 2. Blood Draw Requirements by Study Visit

		Months After Type 1 Diabetes Diagnosis											
Sample Type	**Blood Collection Tube**	**Baseline Visit***		**3 months**		**6 months**		**12 months**		**18 months**		**24 – 60 months – Every 6 month tests**	
Auto-antibodies/ Serum storage (GAD65, IA-2, ZnT8)	SST (Red)	**4 ml**		**4 ml**		**4 ml**		**4 ml**		**4 ml**		**4 ml**	
		0.4ml tests	1.5ml store	0.4ml tests	1.5ml store	0.4ml tests	1.5ml store	0.4ml tests	1.5ml store	0.4ml tests	1.5ml store	0.4ml tests	1.5ml store
PBMC/ Plasma storage	CPT(Blue/ Black)	**6 ml**		**6 ml**		**6 ml**		**6 ml**		**6 ml**		**6 ml**	
		1-3 vials PBMC	3-4ml store	1-3 vials PBMC	3-4ml store	1-3 vials PBMC	3-4ml store	1-3 vials PBMC	3-4ml store	1-3 vials PBMC	3-4ml store	1-3 vials PBMC	3-4ml store
RNA	ABI (Blue)	**2.5 ml**		**2.5 ml**		**2.5 ml**		**2.5 ml**		**2.5 ml**		**2.5 ml**	
HbA1c	EDTA (Purple or Pink)	**0.25 ml**		**0.25 ml**		**0.25 ml**		**0.25 ml**		**0.25 ml**		**0.25 ml**	
MMTT c-peptide	EDTA (Purple or Pink)	**7.0 ml total**		**7.0 ml total**		**7.0 ml total**		**7.0 ml total**		**7.0 ml total**		**7.0 ml total**	
		1.0ml x 7 timepoints		1.0ml x 7 timepoints		1.0ml x 7 timepoints		1.0ml x 7 timepoints		1.0ml x 7 timepoints		1.0ml x 7 timepoints	
MMTT Glucose	Fluoride (Grey)	**7.0 ml total**		**7.0 ml total**		**7.0 ml total**		**7.0 ml total**		**7.0 ml total**		**7.0 ml total**	
		1.0ml x 7 timepoints		1.0ml x 7 timepoints		1.0ml x 7 timepoints		1.0ml x 7 timepoints		1.0ml x 7 timepoints		1.0ml x 7 timepoints	
HLA	EDTA (Purple or Pink)	**1.0 ml**											
Total Blood Volume		**27.75 ml**		**26.75 ml**		**26.75 ml**		**26.75 ml**		**26.75 ml**		**26.75 ml**	

***TEDDY Cases will use the post-diagnosis visit data from the TEDDY study in lieu of the baseline visit; all items listed are for controls only**

Table 3. Visit Schedule and Summary of Contents

	Months after Type 1 Diabetes Diagnosis						
Sampling Frequency	**Baseline Visit***	**3 months**	**6 months**	**12 months**	**18 months**	**24 – 60 months – Every 6 month tests**	**24 – 60 months – Yearly tests**
Blood Samples Collected	X	X	X	X	X	X	
Registration Form	X+						
Enrollment Form	X+						
Diagnosis of Diabetes Form	X						
Medical History Form	X	X	X	X	X	X	
Demographic Form	X			X			X
Family History Questionnaire	X						
Diabetes Management	X	X	X	X	X	X	
Physical Exam	X	X	X	X	X	X	
Continuous Glucose Monitoring		X	X	X	X	X	
Stool		X†					
PedsQL for parents (complete age appropriate form)	X	X	X	X			X
PedsQL for children (complete age appropriate form)	X^	X^	X^	X^			X^
STAI for parents and Well being question for parents	X	X	X	X			X
STAI for children	X^	X^	X^	X^			X^
PIP for parents	X	X	X	X			X

*** For cases TEDDY Study post-diagnosis visit data will be used in lieu of the follow-up study baseline visit; all items listed are for controls only.**
+ Registration and Enrollment forms for TEDDY cases are not completed as part of the TEDDY post-diagnosis visit; these forms must be completed for the TEDDY cases within 3 months of diagnosis.
^ Should only be completed by children 8 years of age and older.
† For cases TEDDY Study diagnosis and post-diagnosis visit data will be used in lieu of the follow-up study stool sample collection; a one-time stool sample will be collected from controls within 3 months of T1D diagnosis (by the end of the 3 month visit window)

13.2. Visit Schedule, Scheduling Windows and Missed Visits

All study visits will be based on the date of diagnosis of type 1 diabetes for the participant. The baseline visit for control participants should occur within 3 months of diagnosis. For

TEDDY cases, their post-diagnosis TEDDY visit will be used in lieu of the baseline visit for this study. The Participant's Details Page for the controls will start with the baseline visit and the Participant's Details Page for the cases will start with the 3 month visit. After that subjects will be seen for a 3 month, 6 month, 12 month, 18 month, 24 month, 30 month and 36 month visit. If there remains C-peptide at the 36 month visit the subject will be followed every 6 months until the disappearance of C-peptide response (subjects will be followed until stimulated c-peptide is <0.05 ng/mL) or 60 months post-diagnosis.

NOTE: If a subject's stimulated c-peptide is <0.05 ng/mL, the site should be sure to complete a Change in Study Participation form for the subject by marking "7. Subject's stimulated c-peptide is <0.05 ng/mL" under "Subject/family does not wish to participate further as of. . ."

Table 4 Visit Scheduling Windows and Missed Data Items to be collected if Visit not completed

Visit	Scheduling/Completion Window (all visit windows are based upon the date of type 1 diabetes diagnosis)	Reimbursed Activity Y/N	Data Collection To Be Attempted if Visit Missed
Baseline – for controls only	Date of diagnosis – 2 months after date of diagnosis	Y	Diagnosis of Diabetes form*
		N	Demographic form*
		Y	Family History Questionnaire*
		Y**	Stool kit to control subjects for collection at home by end of 3 month visit
3 month	2.1 months - 4.5 months	Y	Medical History Form (best done as phone interview when visit is missed)
		Y	Diabetes Management Form
		Y	PedsQL for parents
		Y	PedsQL for children+
		Y	STAI for parents & Well being question for parents
		Y	STAI for children+
		Y	PIP for parents
6 month	4.6 months - 9 months	Y	Medical History Form (best done as phone interview when visit is missed)
		Y	Diabetes Management Form
		Y	PedsQL for parents
		Y	PedsQL for children+
		Y	STAI for parents & Well being question for parents
		Y	STAI for children+
		Y	PIP for parents
12 month	9.1 months – 15 months	Y	Medical History Form (best done as phone interview when visit is missed)
		Y	Diabetes Management Form

		N	Update form for Demographic Data
		Y	PedsQL for parents
		Y	PedsQL for children+
		Y	STAI for parents & Well being question for parents
		Y	STAI for children+
		Y	PIP for parents
18 month	15.1 months – 21 months	Y	Medical History Form (best done as phone interview when visit is missed)
		Y	Diabetes Management Form
24 month	21.1 months – 27 months	Y	Medical History Form (best done as phone interview when visit is missed)
		Y	Diabetes Management Form
		N	Update form for Demographic Data
		Y	PedsQL for parents
		Y	PedsQL for children+
		Y	STAI for parents & Well being question for parents
		Y	STAI for children+
		Y	PIP for parents
30 month	27.1 months – 33 months	Y	Medical History Form (best done as phone interview when visit is missed)
		Y	Diabetes Management Form
36 months	33.1 months – 39 months	Y	Medical History Form (best done as phone interview when visit is missed)
		Y	Diabetes Management Form
		N	Update form for Demographic Data
		Y	PedsQL for parents
		Y	PedsQL for children+
		Y	STAI for parents & Well being question for parents
		Y	STAI for children+
		Y	PIP for parents
42 month	39.1 months – 45 months	Y	Medical History Form (best done as phone interview when visit is missed)
		Y	Diabetes Management Form
48 month	45.1 months – 51 months	Y	Medical History Form (best done as phone interview when visit is missed)
		Y	Diabetes Management Form
		N	Update form for Demographic Data
		Y	PedsQL for parents
		Y	PedsQL for children+
		Y	STAI for parents & Well being question for parents
		Y	STAI for children+
		Y	PIP for parents
54 month	51.1 months – 57 months	Y	Medical History Form (best done as phone interview when visit is missed)

		Y	Diabetes Management Form
60 month	57.1 months – 63 months	Y	Medical History Form (best done as phone interview when visit is missed)
		Y	Diabetes Management Form
		N	Update form for Demographic Data
		Y	PedsQL for parents
		Y	PedsQL for children[+]
		Y	STAI for parents & Well being question for parents
		Y	STAI for children[+]
		Y	PIP for parents

* The site should make all efforts to complete the baseline visit for controls, however if this is not possible the subject can be enrolled on the study up to 3 months from diagnosis at the 3 month visit; if the baseline visit is missed these data items can be collected at the 3 month visit.

Y** = reimbursed for stool sample received by Repository, not for kit given out.

[+]If child is at least 8 years old

13.3. HbA1c data collection at one year and two years after loss of c-peptide

The goal is to follow all subjects until loss of C-peptide production (identified by a <0.05 ng/mL stimulated c-peptide). HbA1c data will be collected at one year and two years after loss of c-peptide production. It is understood that the HbA1c date of collections may not fall exactly at one and two years after the loss of c-peptide. The site should enter whatever data is available to them on these forms even if the date of collection is not exactly one year and/or two years since the loss of c-peptide (as long as it is in the range of +/- 6 months).

This form can be found under the "Additional Study Forms" drop-down menu on the subject's Participant's Details Page:

1. Click on "Enter/Edit/View" link under "Data Management" on the left navigational toolbar.
2. Search for the desired subject.
3. Under "Search Results", click on the Local Code of the desired subject.
4. Choose "HbA1c data collection at 1 year and 2 years after loss of c-peptide" that is in the 'Additional Study Forms' dropdown menu at the upper right-hand corner of the Participant's Details Page.
5. Click 'Select Form' button that is below dropdown menu.
6. Enter information, click the Save button and close the form.

Once the Participant's Details Page has been refreshed, you will see "HbA1c data collection at 1 year and 2 years after loss of c-peptide" 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 "HbA1c data collection at 1 year and 2 years after loss of c-peptide" that have been saved for this subject.
3. Click on an 'event date' link to open up a specific form for this subject.

Data collected on this form:

1. HbA1c result and date
2. Assay type
3. Machine type

13.4. Rewards information will be the same as TEDDY – see TEDDY MOO section 13.10 for details

13.5. Preparation for future visits will be the same as TEDDY – see TEDDY MOO section 13.11 for details

14. Adverse Event Reporting will be the same as TEDDY – see TEDDY MOO sections 9.6 and 13.12 for details

14.1. Adverse Event Reporting Timeline

Within *24 hours* (of learning of the event), investigators must report any reportable Serious Adverse Event (SAE) that: Is considered life-threatening/disabling or results in death of subject -OR- Is Unexpected/Unanticipated

Investigators must report all other reportable SAEs within *5 working days* (of learning of the event).

All other (suspected) reportable AEs must be reported to the coordinating center within *20 working days* of the notification of the event or of the site becoming aware of the event.

Local institutional reporting requirements to IRBs, any GCRC oversight committee remain the responsibility of the treating physician and the Study Chair.

15. Study Forms/Questionnaires

Most of the forms/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 forms/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 child's daily life.

15.1. Administration, Review and Coding will be the same as TEDDY with a few minor changes to meet the details of the Follow-up of Children Diagnosed with Diabetes Study – see TEDDY MOO section 10.3 for details

15.2. Diagnosis of Diabetes Form will be the same as the TEDDY form – see TEDDY MOO section 13.9.1 for details (disregard section on "How to get to the Diagnosis of Diabetes Form")

The cases will complete the Diagnosis of Diabetes form as part of the TEDDY Study; the controls should complete the form at his/her first visit for the Follow-up of Children Diagnosed with Diabetes Study. The Diagnosis of Diabetes form will be available for the controls on the Participant's Details Page under the baseline visit.

15.3. Demographic Form will be the same as the TEDDY 9 month Interview except that questions 11-16 have been removed from the form for the Follow-up of Children Diagnosed with Diabetes Study – see TEDDY MOO sections 10.4.9.1. – 10.4.9.3. for details

This form is intended to be interviewer administered at the first visit for control participants only. For TEDDY cases, the participant's 9 month Interview and Update Form for Primary Caretaker data completed during the TEDDY study will be used at analysis time. 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 child lives with one parent part of the time and the other parent the other part of the time.

An Update form for Demographic Data will be collected from all subjects at the 12 month, 24 month, 36 month, 48 month and 60 month visits. These forms will be prepopulated with the data from the last submitted form, just as it is in TEDDY for the Update form for Primary Caretaker – see TEDDY MOO section 10.4.10 for details.

15.4. Family History Questionnaire will be the same as TEDDY – see TEDDY MOO sections 10.4.7.1. – 10.4.7.3 for details

This questionnaire is intended to be given to control participants at the first visit and brought back with them at the next visit or mailed back to the site in a postage paid envelope. For TEDDY cases, the participant's 9 month Family History Questionnaire and Update Form for Family History Questionnaire completed during the TEDDY study will be used at analysis time.

> NOTE: As the TEDDY Update Form for Family History Questionnaire was not ready for use until June 2012 there may be some cases enrolled in the Follow-up study who have not had an Update Form for Family History Questionnaire completed yet or some cases who have not completed an Update Form for Family History Questionnaire within the last two years. In these instances the site should complete the next due Update Form for Family History Questionnaire through the case's **TEDDY** Participant's Details Page (not the case's JDRF Follow-up Study Participant's Details Page).

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.

15.5. Diabetes Management Form

The Diabetes Management Form is designed to be completed at the TEDDY post-diagnosis visit for case subjects and at the baseline visit for control subjects and for all subjects at the 3 month, 6 month, 12 month, 18 month, 24 month and every 6 months thereafter.

15.5.1. 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.

15.5.2. Administration of the Diabetes Management Form

During each 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 A "Glucose Monitoring" question #1 asks "Does your child use a Continuous Glucose Monitoring System (CGMS)?". When a flash glucose monitor (FGM)is used, "Yes" should be indicated to this question.
- 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
    - 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
    - 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
- 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. The first time the form is administered to a case or control subject the questions in section D should be answered since diagnosis. At all visits thereafter the questions in section D should be answered as the question is worded (since the last visit).

15.6. Medical History Form contains questions extracted from the TEDDY Book Extraction Form – see TEDDY MOO section 11 Allergies section, Weight and Height section, Illnesses section, Medications section and Hospitalizations section for details as well as information directly below

The Medical History Form asks for data on instances that have occurred since the last visit. The first time the form is administered to a control subject will be the first visit therefore the wording of the question "since the last visit" would not apply in this instance. The first time that the Medical History Form is administered to a control subject, use the time frames listed below for each question.

- Allergies (question #1): collect data from birth to present time
- Weight and Height (question #2): collect the most current measurement completed by the health care provider
- Acute illnesses (question #3a): collect data from last 3 months to present time
- Chronic illnesses (question #3b): collect data from birth to present time
- Medications (question #4): collect data from last 3 months to present time
- Hospitalizations (question #5): collect data from last 3 months to present time

Question #6 of the Medical History Form "Diagnosis of DKA" is a new question and is n ot asked in the TEDDY Study. This question asks for the following information:

- Date of diagnosis of DKA
- Initial blood glucose value (this should be the blood glucose that is completed at the same time as the initial pH and initial bicarbonate)
- Initial pH
- Initial bicarbonate
- Beta OHB (blood ketone levels)

15.7. Psychosocial Questionnaires

Past research has suggested that many children and parents experience psychological distress following a diagnosis of type 1 diabetes (Stoppelbein & Greening, 2007). However, TEDDY participants who develop diabetes may have a different experience than those who develop diabetes in the general population due to a number of factors. First, there is preliminary evidence to suggest that TEDDY participants who develop diabetes are diagnosed earlier in their disease course than community controls, which often prevents hospitalization and diabetic ketoacidosis. Second, TEDDY families, due to their participation in the study, have some awareness of their increased risk for diabetes which may lessen the shock families often report at diagnosis (Lowes, Gregory, & Lyne, 2004). Finally, TEDDY families have consistent, ongoing contact with TEDDY staff which may help them develop greater familiarity with the medical system. Given these differences, TEDDY families may experience less distress and may have improved psychosocial outcomes compared to families of children diagnosed with diabetes in the general population. To date, no studies have prospectively compared psychological distress in families of children diagnosed with diabetes aware of their risk status to that of families within the general population.

We also hypothesize that TEDDY children who are diagnosed earlier in the course of the disease (prior to diabetic ketoacidosis and symptoms) will have better health-related quality of life and psychological functioning than their TEDDY peers diagnosed later in the course of the disease. We also predict that parents of TEDDY children diagnosed earlier will also have better health-related quality of life, psychological functioning, and less parenting stress.

The aim of this study is to compare the psychosocial functioning of children diagnosed with type 1 diabetes in the TEDDY study to that of children diagnosed in the general population. Specific hypotheses are as follows:

Hypothesis 1. TEDDY children diagnosed with diabetes and their parents will report greater diabetes-specific quality of life than control families.

Hypothesis 2. TEDDY children diagnosed with diabetes will report less psychological distress (depression, anxiety) than control children.

Hypothesis 3. TEDDY parents of children diagnosed with diabetes will report less psychological distress (depression, anxiety, pediatric parenting stress) than control parents.

Hypothesis 4: TEDDY children who are diagnosed earlier in the course of the disease will have better health-related quality of life and psychological functioning than those TEDDY cases diagnosed later in the course of the disease. We also predict that parents of TEDDY children diagnosed earlier will also have better health-related quality of life, psychological functioning, and less parenting stress.

Methods

Procedure

Participant's primary caregiver will complete psychosocial questionnaires at the baseline (controls only), 3, 6, 12, 24 month visits and subsequent annual visits. If two caregivers are present at the study visit, they will each complete the measures. The same caregiver will complete the measures at each visit. Children will complete psychosocial questionnaires if they are at least 8 years old and have completed the assent process when required by their institution (the assent process for each participant will be completed at an appropriate age as determined by the local IRB/Ethics board for each participating center). Questionnaires should take approximately 15-30 minutes for parents to complete and approximately 10-15 minutes for children to complete.

At all study visits, it is preferred that participants complete all measures at the visit. However, at the baseline visit parents will have the option to complete the psychosocial questionnaires at home if there are significant time constraints. In these instances, study sites will provide participants with a self-addressed stamped envelope to facilitate the return of the questionnaires. Participants will be instructed to return the questionnaires within two weeks of their visit. Study staff will contact the parent by phone at the end of the two week window if the questionnaires have not been received. At that time, study staff will administer the questionnaires by phone.

15.7.1. PedsQL for parents and PedsQL for children (complete age appropriate form)

Disease-specific quality of life. Caregivers and children aged 8 and older will complete the diabetes module of the Pediatric Quality of Life Inventory (PedsQL 3.2 Type 1 Diabetes; Varni, et al., 2003) at the baseline (controls only), 3, 6, 12, 24 month visits and subsequent annual visits. The PedsQL 3.2 Diabetes module was designed to measure diabetes-specific health-related quality of life across the domains of Communication, Treatment barriers, Treatment adherence, Diabetes symptoms, and Worry. This instrument has parent proxy forms developed for use with parents of children aged 2-4 years (toddler), 5-7 years (young child), 8-12 years (child) and 13-18 years (teen) and child-report forms for ages 8-12 years (child) and 13-18 years (teen) will be used in TEDDY. The PedsQL 3.0 Diabetes module is currently being used in the DAISY follow-up study.

Since the version of the parent and child PedsQL forms that are administered are based upon the age of the child, the DCC has programmed its system to display the corresponding age-group form on the Participant's Details Page based upon the child's date of birth. If a child's birthday falls in a visit window and overlaps with two age-group forms, both age-group forms will be displayed on the Participant's Details Page. The site should then have the family complete the form version that corresponds to the child's age at the time of the visit.

15.7.2. STAI for parents and STAI for children

Psychological functioning. Parents and children aged 8 and older will complete a 6-item short form of the state portion of the State-Trait Anxiety Inventory (STAI) (Spielberger, 1970) at the baseline (controls only), 3, 6, 12, 24 month visits and subsequent annual visits. This shortened version is currently being used in the TEDDY study. The STAI is a reliable assessment instrument for assessing situation-specific anxiety in the U.S. and internationally. It has been used to assess anxiety following diagnosis of diabetes (Grey, Cameron, Lipman, & Thurber, 1995).

15.7.3. Well-being question for parents

Psychological functioning. In order to measure parent depressive symptoms, parents will complete the 6-item well-being questionnaire that has been used as a part of the current TEDDY study at the baseline (controls only), 3, 6, 12, 24 month visits and subsequent annual visits. These items focus on the most prominent mood and behavioral symptoms associated with depression and serve as a brief, screening questionnaire to identify parents who are struggling with these issues.

15.7.4. PIP for parents

Pediatric parenting stress. Parents will complete the 42-item Pediatric Inventory for Parents (PIP; Streisand, Braniecki, Tercyak, & Kazak, 2001), which measures stress related to having a child with a chronic illness at the baseline (controls only), 3, 6, 12, 24 month visits and subsequent annual visits. The PIP assesses four domains of

health-related parenting stress (Communication, Emotional distress, Medical care, Role function) across 2 scales: Frequency (F) of stress and Difficulty (D) of stress. The PIP has been used with parents of newly diagnosed children with diabetes (Streisand, 2008) and has shown good psychometric properties (Streisand, et al., 2001). The PIP has also been successfully translated into Spanish (del Rincón, Remor, & Arranz, 2007).

15.8. Form/Questionnaire General Training Requirements will be the same as TEDDY – see TEDDY MOO section 10.5 for details

16. Height and Weight Measurements will be the same as TEDDY – see TEDDY MOO section 13.2 – 13.3 for details

17. Blood Samples

Venous blood will be drawn for processing for serum, plasma, PBMCs, RNA, HbA1c, MMTT and HLA testing. 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 5). The volumes reflect both the scientific needs of the study and the experience of the TEDDY clinical centers.

Table 5 Optimal Blood Volumes at Each Clinic Visit

Clinic Visit	Optimal Total Blood Volume
Baseline*	27.75 ml
3 months after T1D diagnosis	26.75 ml
6 months after T1D diagnosis	26.75 ml
12 months after T1D diagnosis	26.75 ml
18 months after T1D diagnosis	26.75 ml
24 months after T1D diagnosis	26.75 ml
30 months after T1D diagnosis	26.75 ml
36 months after T1D diagnosis	26.75 ml
42 months after T1D diagnosis	26.75 ml
48 months after T1D diagnosis	26.75 ml
54 months after T1D diagnosis	26.75 ml
60 months after T1D diagnosis	26.75 ml

*TEDDY Cases will use the post-diagnosis visit data from the TEDDY study in lieu of the baseline 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. MMTT (c-peptide, glucose)
2. Autoantibodies

3. HbA1c
4. PBMC
5. RNA
6. HLA
7. Storage

17.1. Venous blood draw procedures will be the same as TEDDY with a few minor changes to meet the details of the Follow-up of Children Diagnosed with Diabetes Study – see TEDDY MOO section 13.4.1. for details

The appropriate size and number of collection tubes for each visit on the Follow-up of Children Diagnosed with Diabetes Study are detailed in the table below:

Table 6 Number and Size of Collection Tubes for Each Clinic Visit

Clinic Visit	SST	CPT	ABI	EDTA	Oxalate/Fluoride
All Clinic Visits	1 x 7 ml	1 x 8 ml	1 x 10 ml	1 x 2 ml^; 1 x 0.5 ml 7 x 1.2 ml	7 x 1.2 ml

^ = The HLA sample will be drawn from control subjects only one time.

17.2. Capillary blood draw procedures will be the same as TEDDY with a few minor changes to meet the details of the Follow-up of Children Diagnosed with Diabetes Study – see TEDDY MOO section 13.4.2. for details

17.3. Mixed Meal Tolerance Test (MMTT)

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.

A 2 hour MMTT will be performed on every subject at every study visit.

NOTE: Should a subject refuse to complete the MMTT at the initial study visits (baseline and/or 3 month visit) it has been approved that the first MMTT can be completed at the 6

month visit, but as a study requirement the latest the first MMTT can be performed is at the 6 month visit.

Mixed Meal Dose: The test meal (Boost High Protein) is given at a dose of 6 mL per kilogram body weight. Maximum dose is 360 mL. Boost High Protein 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 High Protein®, 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 High Protein 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 High Protein®, 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 High Protein Dose: • 6 mL/kg up to a maximum of 360 mL. BOOST High Protein cans contain 8 fluid-ounces (240 mL) **BOOST High Protein Dose Calculation** Subject's weight in pounds_____ multiply by 0.454 = _____kg Subject's weight in kg _____ multiply by 6 = _____ mL of BOOST High Protein (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 High Protein Dose Given: _____**mLs** (BOOST High Protein dose in mL)

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 High Protein - this is the "0 minute" sample.
c. Meal consumption - Start the clock at the beginning of the drink. The dose of Boost High Protein 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 High Protein		
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 (be sure to have gluten-free snacks available).

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.

18. Stool Sample Collection– will be the same as TEDDY – see TEDDY MOO section 15 for details.

For cases, stool sample data collected during the TEDDY Study diagnosis and post-diagnosis visits will be used.

For controls, the child's parent(s) will collect a one-time stool sample of at least 5g of the child's stool within 3 months of the diagnosis of type 1 diabetes (by the end of the 3 month visit window). Samples will be collected in the three plastic stool containers provided by the clinical center.

In the United States, parents will send the containers at either ambient or +4°C temperature with guaranteed delivery within 24 hours in the appropriate shipping box to the NIDDK repository. In Europe, parents will send the containers at ambient or +4°C temperature with guaranteed delivery within 24 hours in the appropriate shipping box to the local center they are affiliated with. The European clinical center will store the stool samples and will send monthly bulk shipments of frozen stool to the NIDDK Repository.

19. Continuous Glucose Monitoring (CGM)

Within this study, participants will be asked to complete a 5-7 day (minimum 72 hours) period of continuous glucose monitoring immediately after the visit with MMTT assessment of C-peptide, using continous glucose monitors (CGM), other CGMs or flash glucose monitors (FGM). (Sites should still upload the CGM data to the TEDDY website even if the data was collected for less than 72 hours.) This will occur following the 3 month, 6 month, 12 month, 18 month, 24 month, 30 month, 36 month, 42 month, 48 month, 54 month and 60 month visits. Participants may opt not to participate in the continuous glucose monitoring. This will not affect the participant's ability to participate in the study.

We anticipate that less than 5% of the participants will be using their own CGM at that time and they will not be switched to the study CGM sensor for the period. An increase in use of the FGM devices may also be noted in some areas. A CGM transmitter and receiver, sensors* and in-person training by the study research nurse will be provided to the study participants on the day of the visit by a certified CGM trainer. In addition, the research nurse will be available by pager to answer questions or assist with problems during the 5-7 days of CGM.

* Sites should be aware that CGM sensors expire after 6 months.

Following the observation period, a study physician will review the CGM results with the participant and monitor the results for safety. Patients and their usual diabetes providers will be notified if significant hypoglycemia is observed, following standards used in our clinic. Participants will be given a glucose meter similar to the one they use and be asked to use the study's meter for all glucose measurements for one week while wearing the CGM.

Measures of glycemic control will include HbA1c, the overall mean of glucose values, % of values within target range (60-180 mg/dl), % of values <60 mg/dl (hypoglycemic range), and % of values >180 mg/dl (hyperglycemic). Primary variables to characterize glycemic variability will include the overall standard deviation (SD), the mean of daily differences (MODD) and the mean amplitude of glycemic excursions (MAGE). While multiple additional computed measures have been proposed in this dynamically evolving analytical field, they do not appear to offer a particular advantage and we will limit the number of comparisons to reduce the chance of type I error.

Please note the following for the Dexcom Gen-4 Model:

- The Products are intended for single patient use only.
- The Products, including without limitation, the G4 Sensor, Transmitter, and Receiver must be removed prior to Magnetic Resonance Imaging (MRI), CT scan, or diathermy treatment.
- Taking acetaminophen containing products (such as Tylenol) while wearing the sensor may falsely raise your sensor glucose readings. The level of inaccuracy depends on the amount of acetaminophen active in your body.
- Trial subjects should update the Product's calibration every 12 hours at a minimum. The performance of the Product when calibrated less frequently than every 12 hours has not been studied and the readings may be inaccurate.

19.1.1. CGM file export process

19.1.1.1. Dexcom Seven-Plus Model

1. Go to TOOLS
2. Export DATA
3. SELECT PATIENT FROM DROPDOWN
4. SELECT DATES: CHOOSE START DATE
5. DATA FORMAT: TAB DELIMITED TEXT
6. SELECT EXPORT
7. SAVE as a .TXT FILE
8. Right click on FILE
9. OPEN WITH EXCEL
10. DELETE PATIENT NAME TO PROTECT ID
11. ADD SUBJECT ID AND LOCAL ID
12. Date of Birth in DD/MON/YEAR FORMAT
13. PATIENT IDENTIFIER (VISIT #_DATE OF VISIT in DD/MON/YEAR format)
14. UPLOAD TO THE DCC

19.1.1.2. Dexcom G4 Model

1. Open Dexcom Studio
2. Select PATIENT
3. Select patientfile
4. Export DATA
5. SELECT EXPORT: choose all or start time
6. Save as a .TXT file
7. Open with Excel
8. Select DATA
9. Select FROM TEXT
10. Select the file
11. Add SUBJECT ID and LOCAL ID
12. Date of Birth in DD/MON/YEAR format
13. PATIENT IDENTIFIER (VISIT# DATE OF VISIT IN DD/MON/YEAR format)
14. Select IMPORT, NEXT, NEXT, FINISH
15. Select IMPORT DATA
16. Select FILE

17. SAVE AS
18. SAVE AS TYPE: CSV file

19.1.2. CGM data upload

In order to allow data uploads for various models of CGMs, there is no required format for the CGM file that the site will upload to the DCC. However the site must be sure to remove all direct subject identifiers (name, initials, etc) from the file they upload to the study website as the DCC cannot receive direct subject identifiers. The CGM file you upload must be either a CSV or XLS file, there is no required naming convention for the file.

1. Login to the TEDDY website, go to the "Protocols" section and click on "JDRF FOLLOW-UP"
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. Open Continuous Glucose Monitoring upload form which can be found on the Participant's Details Page under the corresponding visit. Make sure to upload the file to the correct visit. The system cannot check this.
6. Click "Browse" in order to locate the CGM file you would like to upload.
7. Click on the file you would like to upload then click "Open"
8. You will see the name of the file you have selected will be prepopulated in the "File" and "File Description" fields. If you would like to title the file something different you can edit the "File Description" field.
9. "File Type" will be prepopulated with CSV/XLS
10. "Creation/Capture Date" will be prepopulated with the date you upload the file to the website
11. Click "Save" and the CGM data will then be imported into the DCC's database
    a. If a file is uploaded to an incorrect subject or visit contact the DCC in order to delete the data from the DCC database

19.1.3. CGM Device Information Form

In association with each Continuous Glucose Monitoring data file upload, sites should complete the CGM Device Information Form that corresponds with the visit the CGM data was collected. The site will collect information regarding the model of the CGM device used, and indicate whether or not the device was blinded during the data collection.

1. Login to the TEDDY website, go to the "Protocols" section and click on "JDRF FOLLOW-UP"
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. Open CGM Device Information Form which can be found on the Participant's Details Page under the corresponding visit.
6. Enter the date the form was completed.
7. Choose the visit location code from the drop down menu.
8. Enter the TEDDY Staff Code of the person completing the form.
9. Select the CGM Device Type from these options:
    - Dexcom G4 Platinum
    - Dexcom Seven Plus
    - Freestyle Libre
    - Medtronic Enlite sensor
    - Medtronic Guardian REAL-Time
    - Other (if other is chosen, a code box will be provided to enter the assigned TEDDY code)
    - Unknown
10. Indicate whether the device data was blinded during collection.
11. Click "Save" once the form is complete.

20. Laboratory Measurements

20.1. Serum – SST Tube will be the same as TEDDY– see TEDDY MOO section 14.1.1., except for the Serum aliquoting section - see below instead

To be collected from all subjects at all visits.

Serum aliquoting

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. Any additional serum into a 2.0 ml cryovial with a gray insert for storage at the repository

20.2. PBMC – CPT Tube will be the same as TEDDY– see TEDDY MOO section 14.1.2. "Isolation and Cryopreservation of PBMC from CPT tube with prior plasma harvest", except for population to be collected from - see below instead

To be collected from all subjects at all visits.

20.3. RNA – ABI Tube will be the same as TEDDY– see TEDDY MOO section 14.1.3.

To be collected from all subjects at all visits.

20.4. Whole Blood for HLA Sample – EDTA Tube (for additional HLA genotyping only) will be the same as TEDDY – see TEDDY MOO section 14.1.4., except for population to be collected from – see below instead

To be collected from control subjects only at the first clinic visit.

20.5. HbA1c – EDTA tube will be the same as TEDDY – see TEDDY MOO section 14.1.5., except for population to be collected from – see below instead

To be collected from all subjects at all visits.

20.6. Blood Sample Collection Forms (SCFs) will be the same as TEDDY – see TEDDY MOO section 14.1.7. "Enter/Edit/View Link" for details, disregard the Long-Distance protocol instructions as it won't be used in this study

20.6.1. 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. Login to the TEDDY website, go to the "Protocols" section and click on "JDRF FOLLOW-UP"
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. Open MMTT SCF
6. Subject ID, Local Code, and Clinical Center fields will be prepopulated on the Sample Collection Form
7. Choose the visit location code from the drop down menu and enter the Date of Draw (DD/MMM/YYYY) on this form.
8. 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).
9. 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 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.
12. In the provided space, enter the sample volume (mL) contained in the cryovial.
13. In the provided space enter box number and space number where the sample will be stored.
14. 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
    a. 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.
15. Repeat steps 9-14 as necessary.
16. When all information for this specific SCF has been entered, click the "Save Form" button at the top of this form.
17. Store the samples at -70°C. Send samples to the MMTT 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.

21. Shipping

21.1. Samples shipped to the Repository (Autoantibody Repository samples, PBMC samples, serum storage samples, plasma storage samples) will be the same as TEDDY– see TEDDY MOO section 14.1.8.1. for details

21.2. Blood samples shipped to the Autoantibody Reference Labs will be the same as TEDDY– see TEDDY MOO section 14.1.8.2. for details

21.3. Blood samples shipped to the HLA Reference Lab will be the same as TEDDY – see TEDDY MOO section 14.1.8.3. for details

21.4. Blood samples shipped to the RNA Lab will be the same as TEDDY– see TEDDY MOO section 14.1.8.4. for details

21.5. Blood samples shipped to the HbA1c Lab will be the same as TEDDY – see TEDDY MOO section 14.1.8.5. for details

21.6. Blood samples shipped to the MMTT Lab

Entering information into the "Sample Shipment System"

Once a month each clinical center will send bulk shipments of MMTT samples to the MMTT lab.

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 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 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 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:
    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 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 Lab address

      Specimen Processing
      Northwest Lipid Metabolism and Diabetes Research Laboratories
      University of Washington
      401 Queen Anne Ave North
      Seattle, WA 98109
      USA
      Phone 206-616-6474

   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 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

22. Autoantibody Results Notification will be the same as TEDDY – see TEDDY MOO section 16.1. for details

23. Data Entry and Management

23.1. Enter/Edit/View will be the same as TEDDY– see TEDDY MOO section 17.1.2. for details

23.2. How to clear unwanted radio button choices will be the same as TEDDY – see TEDDY MOO section 17.1.3. for details

23.3. Error messages displayed in online data entry forms and Sample Collection Forms will be the same as TEDDY – see TEDDY MOO section 17.1.4. for details

23.4. Data Upload will be the same as TEDDY – see TEDDY MOO section 17.1.7. for details

23.5. Search by Vial Barcode Number will be the same as TEDDY – see TEDDY MOO section 17.1.10. for details

23.6. Standard data collection forms

23.6.1. Downloading blank teleforms will be the same as TEDDY – see TEDDY MOO section 17.2.1. for details

23.6.2. Downloading and printing prepopulated forms (single copy) will be the same as TEDDY – see TEDDY MOO section 17.2.2. for details

23.6.3. Downloading & printing prepopulated forms (several at a time) will be the same as TEDDY – see TEDDY MOO section 17.2.3. for details

23.7. Instructions for using the TEDDY Code Book will be the same as TEDDY – see TEDDY MOO section 17.2.4. for details

23.8. Scanning Forms will be the same as TEDDY – see TEDDY MOO section 17.2.5. for details

23.9. Submitting Form data will be the same as TEDDY – see TEDDY MOO section 17.2.6. for details

23.10. Viewing/Editing online data will be the same as TEDDY – see TEDDY MOO section 17.2.7. for details

23.11. Tracking System will be the same as TEDDY – see TEDDY MOO section 17.2.8. for details

23.12. Instructions for using the Change in Study Participation Form will be the same as TEDDY – see TEDDY MOO section 17.2.10. for details

23.13. Instructions for using the Participant in Non-TEDDY Research Form will be the same as TEDDY – see TEDDY MOO section 17.2.13 for details

24. 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.

24.1. HLA Confirmation Sample

- $91 per sample for samples analyzed prior to July 1, 2014 and $164.75 for samples analyzed on or after July 1, 2014 to the HLA Reference Laboratory
    - To be paid once the samples are run by the lab and the results are received by the DCC.

24.2. Clinic Visit Blood Draws

- $51.50 for any amount of blood drawn – includes the following tests
    - Autoantibodies
    - Autoantibodies – QC and confirmation
    - HbA1c
    - HLA confirmation
    - PBMC
    - mRNA
    - Serum storage
    - Plasma storage
- 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 Table 7 for list of unusable reasons)

24.3. Questionnaires

- $103 per clinic visit for all **completed** questionnaires at that visit
- 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 the questionnaires reimbursement.

Baseline Visit*:

Diagnosis of Diabetes Form**
- The date of Diagnosis by ADA criteria must fall within the visit window
- Fields required for completeness – Date of Diagnosis by ADA criteria

Family History Questionnaire**
- Fields required for completeness – at least one question, any question

Medical History Form
- The interview date must fall within the visit window
- Fields required for completeness – 1, 3a, 3b, 4 and 5

Diabetes Management form
- The interview date must fall within the visit window
- Fields required for completeness – all questions on the form

* For cases TEDDY Study post-diagnosis visit data will be used in lieu of the follow-up study baseline visit; all items listed are for controls only. TEDDY cases will be reimbursed for the post-diagnosis visit through the TEDDY study.

**All four forms are required for the reimbursement of the baseline visit. The Diagnosis of Diabetes Form and the Family History Questionnaire must be completed before the baseline visit can be reimbursed. In instances when the Diagnosis of Diabetes Form is not completed until the 3 month visit and Family History Questionnaire is not completed until the 3 month or 6 month visit, baseline visit reimbursement will be held pending completion of the forms.

3 month visit:

Medical History Form
- The interview date must fall within the visit window
- Fields required for completeness – 1, 3a, 3b, 4 and 5

Diabetes Management form
- The interview date must fall within the visit window
- Fields required for completeness – all questions on the form

6 month visit:

Medical History Form

- The interview date must fall within the visit window
- Fields required for completeness – 1, 3a, 3b, 4 and 5

Diabetes Management form

- The interview date must fall within the visit window
- Fields required for completeness – all questions on the form

12 month visit:

Medical History Form

- The interview date must fall within the visit window
- Fields required for completeness – 1, 3a, 3b, 4 and 5

Diabetes Management form

- The interview date must fall within the visit window
- Fields required for completeness – all questions on the form

18 month visit:

Medical History Form

- The interview date must fall within the visit window
- Fields required for completeness – 1, 3a, 3b, 4 and 5

Diabetes Management form

- The interview date must fall within the visit window
- Fields required for completeness – all questions on the form

24 month visit:

Medical History Form

- The interview date must fall within the visit window
- Fields required for completeness – 1, 3a, 3b, 4 and 5

Diabetes Management form

- The interview date must fall within the visit window
- Fields required for completeness – all questions on the form

30 month visit:

Medical History Form

- The interview date must fall within the visit window
- Fields required for completeness – 1, 3a, 3b, 4 and 5

Diabetes Management form

- The interview date must fall within the visit window
- Fields required for completeness – all questions on the form

36 month visit:

Medical History Form

- The interview date must fall within the visit window
- Fields required for completeness – 1, 3a, 3b, 4 and 5

Diabetes Management form

- The interview date must fall within the visit window
- Fields required for completeness – all questions on the form

42 month visit:

Medical History Form

- The interview date must fall within the visit window
- Fields required for completeness – 1, 3a, 3b, 4 and 5

Diabetes Management form

- The interview date must fall within the visit window
- Fields required for completeness – all questions on the form

48 month visit:

Medical History Form

- The interview date must fall within the visit window
- Fields required for completeness – 1, 3a, 3b, 4 and 5

Diabetes Management form

- The interview date must fall within the visit window
- Fields required for completeness – all questions on the form

54 month visit:

Medical History Form

- The interview date must fall within the visit window
- Fields required for completeness – 1, 3a, 3b, 4 and 5

Diabetes Management form

- The interview date must fall within the visit window
- Fields required for completeness – all questions on the form

60 month visit:

Medical History Form

- The interview date must fall within the visit window
- Fields required for completeness – 1, 3a, 3b, 4 and 5

Diabetes Management form

- The interview date must fall within the visit window
- Fields required for completeness – all questions on the form

24.4. Quality of Life Questionnaires

- $50 per clinic visit for all **completed** Quality of Life questionnaires at that visit
- 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.

Baseline Visit*:

PEDsQL for parents

- The date form completed must fall within the visit window
- 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)

- The date form completed must fall within the visit window
- Fields required for completeness – at least 50% of all questions on the form must be answered

STAI and Well-being question for parents

- The date form completed must fall within the visit window
- 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)

- The date form completed must fall within the visit window
- Fields required for completeness – all questions must be answered

PIP

- The date form completed must fall within the visit window
- 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

* All items listed are for controls only.

3 month visit:

PEDsQL for parents

- The date form completed must fall within the visit window
- 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)

- The date form completed must fall within the visit window
- Fields required for completeness – at least 50% of all questions on the form must be answered

STAI and Well-being question for parents

- The date form completed must fall within the visit window
- 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)

- The date form completed must fall within the visit window
- Fields required for completeness – all questions must be answered

PIP

- The date form completed must fall within the visit window
- 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

6 month visit:

PEDsQL for parents

- The date form completed must fall within the visit window
- 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)

- The date form completed must fall within the visit window
- Fields required for completeness – at least 50% of all questions on the form must be answered

STAI and Well-being question for parents

- The date form completed must fall within the visit window
- 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)

- The date form completed must fall within the visit window
- Fields required for completeness – all questions must be answered

PIP

- The date form completed must fall within the visit window
- 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

12 month visit:

PEDsQL for parents

- The date form completed must fall within the visit window
- 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)

- The date form completed must fall within the visit window
- Fields required for completeness – at least 50% of all questions on the form must be answered

STAI and Well-being question for parents

- The date form completed must fall within the visit window
- 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)

- The date form completed must fall within the visit window
- Fields required for completeness – all questions must be answered

PIP

- The date form completed must fall within the visit window

- 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

24 month visit:

PEDsQL for parents

- The date form completed must fall within the visit window
- 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)

- The date form completed must fall within the visit window
- Fields required for completeness – at least 50% of all questions on the form must be answered

STAI and Well-being question for parents

- The date form completed must fall within the visit window
- 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)

- The date form completed must fall within the visit window
- Fields required for completeness – all questions must be answered

PIP

- The date form completed must fall within the visit window
- 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

36 month visit:

PEDsQL for parents

- The date form completed must fall within the visit window
- 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)

- The date form completed must fall within the visit window
- Fields required for completeness – at least 50% of all questions on the form must be answered

STAI and Well-being question for parents

- The date form completed must fall within the visit window
- 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)

- The date form completed must fall within the visit window
- Fields required for completeness – all questions must be answered

PIP

- The date form completed must fall within the visit window
- 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

48 month visit:

PEDsQL for parents

- The date form completed must fall within the visit window
- 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)

- The date form completed must fall within the visit window
- Fields required for completeness – at least 50% of all questions on the form must be answered

STAI and Well-being question for parents

- The date form completed must fall within the visit window
- 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)

- The date form completed must fall within the visit window
- Fields required for completeness – all questions must be answered

PIP

- The date form completed must fall within the visit window
- 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

60 month visit:

PEDsQL for parents

- The date form completed must fall within the visit window
- 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)

- The date form completed must fall within the visit window
- Fields required for completeness – at least 50% of all questions on the form must be answered

STAI and Well-being question for parents

- The date form completed must fall within the visit window
- 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)

- The date form completed must fall within the visit window
- Fields required for completeness – all questions must be answered

PIP

- The date form completed must fall within the visit window
- 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

24.5. Patient Incentives

- $100 per visit
- Money will be disbursed based on the following criteria:
  - any **completed** questionnaire or **usable** sample done at that visit
  - even if patient misses visit but mails questionnaires or samples

24.6. 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.

24.7. Stool Samples

- $10.30 for 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

Table 7 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

*This list is subject to change.

Appendix

1. Appendix A: Model Informed Consent Form
2. Appendix B: Model Assent Form
3. Appendix C: C-peptide results letter to family (Not preserved)
4. Appendix D: C-peptide results letter to family (Preserved)
5. Appendix E: CGM results letter to family

Appendix A: Model Informed Consent Form

Model Informed Consent to Participate in Research
Information to Consider Before Taking Part in this Research Study

IRB Study # _____

Researchers at [*Institution Name*] study many topics. To do this, we need the help of people who agree to take part in a research study. This form tells you about this research study.
We are asking your child to take part in a research study that is called: *Follow-up of Children Diagnosed with Diabetes.*

The person who is in charge of this research study is [*Person in Charge of Study*]**.** This person is called the Principal Investigator. However, other research staff may be involved and can act on behalf of the person in charge.

The person explaining the research to you may be someone other than the Principal Investigator. [*List other research personnel here as follows*:]
Other research personnel who you may be involved with include: [*List other study personnel who may be obtaining informed consent*].

The research will be done at the University of Colorado (Aurora, CO, USA), University of Turku (Turku, Finland), Lund University (Malmö, Sweden**)**, Pacific Northwest Diabetes Research Institute (Seattle, WA, USA) and the University of South Florida (Data Coordinating Center – Tampa, FL, USA)

This research is being paid for by the Juvenile Diabetes Research Foundation (JDRF).

Purpose of the study
The purpose of this study is to:

- Find out if patients diagnosed with type 1 diabetes while participating on a study (like the TEDDY study) do better controlling their diabetes after diagnosis than patients who are diagnosed with type 1 diabetes through standard clinical care (people not participating on studies).

Study Procedures

If you take part in this study, your child will be asked to:

- During your child's visits we will take some of their blood through a needle in their veins. We will also ask you questions about your child's health and how they are feeling.
- During all of your child's visits, except for the 18 month visit, we will also ask you to complete certain questionnaires. The questions ask about how you are feeling and your reactions to the study.
- When your child is 8 years old or older, we will ask them to complete certain questionnaires. The questions ask about how they are feeling and their reactions to the study.
- During your child's visits we will also do a Mixed Meal Tolerance Test (MMTT) to find out how much insulin their pancreas is still making. Before each MMTT, you will get special instructions about diet and insulin dosing. To make the blood sampling easier for the test, an intravenous needle and plastic tube (IV) will be placed in your child's vein. The IV will be kept in place during the test. Two blood samples taken ten minutes apart (one teaspoon of blood for each sample) will be taken

through the IV. Your child will then be given a drink called Boost High Protein, the "mixed meal". This drink will raise your child's blood sugar and cause their body to produce insulin. After drinking Boost High Protein, one-half teaspoon of blood will be taken through the IV at regular intervals for 2 hours. The total amount of blood taken for the MMTT will not be greater than 2 tablespoons for the two hour test.

- During your 3 month, 6 month, 12 month, 18 month 24 month 30 month, 36 month, 42 month, 48 month, 54 month and 60 month visits, your child will be asked to wear a continuous glucose monitor (CGM), other CGMs or flash glucose monitors (FGM). The CGM is an FDA-approved device that records glucose levels throughout the day and night. A tiny glucose-sensing device, similar to an insulin pump insertion, called a "sensor" is inserted just under the skin. The sensor measures glucose every five minutes and sends this information to the monitor, a pager-sized device that you keep in your pocket or on your waistband. Following the monitoring, a study physician will review the CGM results with you and monitor the results for safety; you and your usual diabetes provider will be notified if significant hypoglycemia is observed. You may opt not to have your child wear the continuous glucose monitor. This will not affect their participation in the study.
- Each visit will take between 3-5 hours. Your child will have an initial visit after diagnosis, then at 3 months, 6 months, 12 months, 18 months, 24 months, and then every 6 months thereafter for up to 10 years.
- [*Please provide a description of the facilities in which the research will be done*]

Informed Consent and Assent

As your child's parent, you must consent to have your child participate in the Follow-up of Children with Diabetes study. When your child is X years old, we will ask for your child's assent or agreement to continue in the study. *[Assent age is site specific]*

Sample Storage

Study samples will be stored at the local site and the central repository. No personal information about you or your child will be given to the central repository. The samples may be used for this study or other research studies.

To be in this study you must agree to store samples in the central repository. You must agree to have these samples used for research.

Alternatives

You have the alternative to choose not to participate in this research study.

Benefits

We don't know if you will get any benefits by taking part in this study. We hope that this research will tell us more about people with type 1 diabetes so that we can better treat diabetes.

Risks or Discomfort

The following risks may occur:

- Blood draw: we will be taking blood through a vein in your child's arm with a needle. There may be some pain, bruising and tenderness at the place where we take the blood.
- Continuous glucose monitoring (CGM) requires the insertion of a small plastic tube with a needle that is then removed. The small plastic tube stays in place for 5-7 days. There is a low risk of

developing a local skin infection at the site of the sensor needle replacement. Itchiness, redness, bleeding and bruising at the insertion site may occur as well as local tape allergies

Compensation

You will receive $100 for each study visit. *[Site specific]*

Privacy and Confidentiality

We must keep your study records private and confidential.
However, certain people may need to see your study records. By law, anyone who looks at your records must keep them completely confidential. The only people who will be allowed to see these records are:

- The research team, including the Principal Investigator, study coordinator, research nurses, and all other research staff**.**
- Certain government and university people who need to know more about the study. For example, individuals who provide oversight on this study may need to look at your records. This is done to make sure that we are doing the study in the right way. They also need to make sure that we are protecting your rights and your safety.) These include:
    - the [*Institution*] Institutional Review Board (IRB) and the staff that work for the IRB. Other individuals who work for this institution that provide other kinds of oversight may also need to look at your records.
    - the Department of Health and Human Services (DHHS) of the USA.
    - The people who paid for this study and the data coordinating center where the data is stored may look at the study records and pertinent portions of your medical records to make sure the study is done in the right way.

We may publish what we learn from this study. If we do, we will not let anyone know your name. We will not publish anything else that would let people know who you are.

Voluntary Participation / Withdrawal

You should only take part in this study if you want to volunteer. You should not feel that there is any pressure to take part in the study, to please the investigator or the research staff. You are free to participate in this research or withdraw at any time. There will be no penalty or loss of benefits you are entitled to receive if you stop taking part in this study.

New information about the study

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

Questions, concerns, or complaints

If you have any questions, concerns or complaints about this study, call [*name of study doctor*] at [*telephone*].
If you have questions about your rights as a participant in this study, general questions, or have complaints, concerns or issues you want to discuss with someone outside the research, call the Division of Research Integrity and Compliance of the [*IRB office*] at [*telephone*].
If you experience an adverse event or unanticipated problem call [*PI / coordinator*] at [*telephone*].

SIGNATURES

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.

_____

Name of Participant ("Study Subject")

_____

Signature of Parent/Legal Representative **Date**

_____

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

_____

Signature of Consenting 2nd Parent Date

Statement of Person Obtaining Informed Consent

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 Informed Consent Date

_____

Printed Name of Person Obtaining Informed Consent

Appendix B: Model Assent Form

MODEL Assent to Participate in Research
Information for Persons under the Age of 18 Who Are Being Asked To Take Part in Research

IRB Study # _____

Title of study: *Follow-up of Children Diagnosed with Diabetes.*

Why am I being asked to take part in this research?
You are being asked to take part in a research study about type 1 diabetes. You are being asked to take part in this research study because the doctors believe you have type 1 diabetes.
If you take part in this study, you will be one of about 130 people in this study.

Who is doing this study?
The person in charge of this study is [*name of investigator*] of [*institutional affiliation*].

What is the purpose of this study?
By doing this study, we hope to learn more about how people like you are doing with type 1 diabetes.

Where is the study going to take place and how long will it last?
The study will be take place at [*state the general facility*]. You will be asked to come to [*state the site where the research will be conducted, including the room if possible and how often*] during the study. Each of those visits will take about 3 to 5 hours.

What will you be asked to do?
- You will be asked questions about how you feel
- You will be asked to let us take some blood from a vein in your arm
- You will be asked to drink a drink called "boost"
- You will be asked to wear a continuous glucose monitor at your 3 month, 6 month, 12 month, 18 month, 24 month, 30 month, 36 month, 42 month, 48 month, 54 month and 60 month visits

What things might happen that are not pleasant?
To the best of our knowledge, the things you will be doing will not harm you or cause you any additional unpleasant experience.

Will I get better if I take part in this study
We cannot promise that you will feel better from taking part in this research.

What other choices do I have if I do not participate?
You can decide that you do not want to be part of this study.

Do I have to take part in this study?

You should talk with your parents or anyone else that you trust about taking part in this study. If you do not want to take part in the study, that is your decision. You should take part in this study because you really want to volunteer.

If you do not think you want to take part in this study, you should talk this over with your parents [*and doctor, nurse, etc., if applicable*] and decide together.

If I don't want to take part in this study, what will happen?

If you do not want to be in the study, nothing else will happen.

Will I receive any rewards for taking part in this study?

You will not receive any reward for taking part in this study.

Who will see the information about me?

Your information will be added to the information from other people taking part in the study so no one will know who you are.

Can I change my mind and quit?

If you decide to take part in the study you still have the right to change your mind later. No one will think badly of you if you decide to quit. Also, the people who are running this study may need for you to stop. If this happens, they will tell you why.

What if I have questions?

You can ask questions about this study at any time. You can talk with your parents or other adults that you trust about this study. You can talk with the person who is asking you to volunteer. If you think of other questions later, you can ask them.

Assent to Participate

The Follow-up of Children Diagnosed with Diabetes Study has been explained to me. I agree to be in TEDDY. I have had a chance to ask questions. If I have more questions I know I can ask the doctor.

_____ _____

Name of person agreeing to take part in the study Date

_____ _____

Name of person providing information to subject Date

Appendix C: C-peptide results letter to family (Not preserved)

DATE:

Dear _____ ,

On (date), your child's C-peptide levels were measured as part of the Follow-Up of Children Diagnosed with Diabetes Study. The results from the Mixed Meal Tolerance Test (MMTT) were as follow:

Fasting C-peptide: _____ ng/ml
Peak C-peptide: _____ ng/ml

C-peptide is a marker used to monitor insulin production. Anyone with a test result greater than or equal to 0.05 ng/ml is still producing some C-peptide. Based on these results, we conclude that your child is no longer producing detectable amount of their own insulin.

No further participation in the Follow-Up Study of Children Diagnosed with Diabetes study is required.

We want to thank you for being a part of this essential research and helping us to learn more about type I diabetes.

If you have any questions or concerns about these results, please contact the (Study Coordinator) at (phone #).

Thank you again for your participation in this study.

Sincerely,

(PI Signature
PI Name and Institution)

Appendix D: C-peptide results letter to family (Preserved)

DATE:

Dear_____,

On (date), your child's C-peptide levels were measured as part of the Follow-Up of Children Diagnosed with Diabetes Study. The results from the Mixed Meal Tolerance Test (MMTT) were as follow:

Fasting C-peptide: _____ ng/ml
Peak C-peptide: _____ ng/ml

C-peptide is a marker used to monitor insulin production. Anyone with a test result greater than or equal to 0.05 ng/ml is still producing some C-peptide. This means that your child is still producing some of his/her own insulin. We will continue to monitor the C-peptide levels at the next study visit.

If you have any questions or concerns, please contact (Study Coordinator) at (phone #).

We will contact you soon to schedule your child's next study visit. Please let us know if there are any changes to your contact information. This will help us to reach you when it is time for the next visit.

Thank you for being a part of this essential research and helping us to learn more about type I diabetes.

Sincerely,

(PI Signature
PI Name and Institution)

Appendix E: CGM results letter to family

To the Parents of:

DATE:

Dear _____and family,

We would like to thank _____on completing his/her continuous glucose monitoring (CGM) as part of his/her participation in the Follow-Up of Children Diagnosed with Diabetes Study. Thank you for being a part of this essential research and helping us to learn more about type I diabetes.

Enclosed are the CGM results for _____ from his/her last study visit. A copy of this report has also been given to Dr. _____. Please contact your diabetes care provider to discuss these results.

If you have any questions or concerns about this letter or the results you have received, please contact the study coordinator, _____at _____.

_____**'s** HbA1c result on **{date}: _____**

We will be contacting you _____ months before you are due for a study visit to schedule an appointment. In the meantime, please let us know if there are any changes in address or phone number. This will help us to reach you when it is time to repeat the tests.

Again, thank you for your participation in this study.

Sincerely,

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