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LONG-TERM INVESTIGATIVE FOLLOW-UP IN TRIALNET (LIFT)

(Protocol TN-16)

Version: 2.0 12FEB2015

Sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Child Health and Human Development (NICHD), the National Center for Research Resources (NCRR), the Juvenile Diabetes Research Foundation International (JDRF), and the American Diabetes Association (ADA)

PREFACE

The TrialNet Type 1 Diabetes Protocol TN16, *Long-Term Investigative Follow-Up in TrialNet (LIFT)*, describes the background, design, and organization of the study. This protocol will be maintained by the TrialNet Coordinating Center at the University of South Florida over the course of the study through new releases of the entire protocol or issuance of updates either in the form of revisions of complete chapters or pages thereof, or in the form of supplemental protocol memoranda.

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1 INTRODUCTION

1.1 Study Overview

Title	Long-Term Investigative Follow-Up in TrialNet (LIFT)
IND Sponsor	NA
Conducted By	TrialNet
Protocol Chair	Jennifer Marks, MD
Study Design and Objective	This is a descriptive study to evaluate the long term effects of participation in TrialNet studies
Study Duration	Subjects will be followed indefinitely.
Major Inclusion Criteria	Prior participation in a TrialNet study

1.2 Statement of Purpose

This protocol describes the background, design, and organization of the *Long-Term Investigative Follow-Up in TrialNet.* The protocol was written by Dr. Jennifer Marks, Chair of the Long-Term Investigative Follow Up in TrialNet Protocol Committee, the TrialNet Chairman's Office, the TrialNet Vice-Chair Office and the TrialNet Coordinating Center at the University of South Florida. Significant changes that occur to this protocol during the course of this study require the formal approval of the TrialNet Executive committee. The study protocol, along with the required informed consent forms, will be approved by each participating institution's Institutional Review Board (IRB) or Ethics Committee prior to implementation/use.

2 BACKGROUND AND SIGNIFICANCE

Type 1 diabetes mellitus is an immune-mediated disease in which insulin-producing beta cells are completely destroyed resulting in life-long dependence on exogenous insulin. The beta cell destruction process begins many years before clinical onset and continues after development of hyperglycemia and diagnosis. At the time of diagnosis, subjects retain a significant amount of beta cell function as measured by C-peptide responses to a mixed meal tolerance test. However, this beta cell function deteriorates after diagnosis with the presumed eventuality of absent function over time. As shown in the Diabetes Control and Complications Trial, the persistence of residual beta cell function (endogenous insulin secretion) has been associated with important clinical outcomes, specifically reduction in severe hypoglycemia and complications. Moreover, the DCCT study demonstrated that better glucose control itself resulted in improved beta cell function. Yet the DCCT data was limited to those with a narrow range of beta cell function at study entry and had only limited information about beta cell function over time. Thus, long term, prospective data relating clinical outcomes with residual beta cell function is not currently available.

Diabetes TrialNet is an international network designed to conduct clinical trials to intervene in the type 1 diabetes disease process. These trials include tests of therapies in individuals at risk for type 1 diabetes to determine whether therapies can delay or prevent the clinical onset of disease (Prevention Trials) as well as studies in individuals with clinical diabetes to determine whether therapies can preserve residual beta cell function (Intervention Trials).

For Prevention Trials, the clinical trial endpoints include progression of disease measured by clinical onset of disease, development of immunological markers such as autoantibodies, or

development of metabolic markers such as impaired insulin secretion or abnormal glucose tolerance as determined by oral glucose tolerance testing (OGTT). For those in Prevention Trials who have developed clinical disease, it is possible that their post-diagnosis clinical course or insulin secretion may have been affected by their participation in a TrialNet clinical trial. As recently published, individuals who present with type 1 diabetes have significantly less beta cell function at diagnosis than those identified through monitoring of at-risk individuals in clinical research protocols such as TrialNet Pathway to Prevention Study.

TrialNet Intervention Trials use measures of insulin secretion at one and two years post diagnosis as clinical trial endpoints. For those in Intervention Trials, longer term follow-up allows for evaluation of duration of effect of therapy on residual beta cell function.

For individuals in either TrialNet Prevention or Intervention Trials, descriptive information may also allow for exploring relationships of such therapies with long term clinically important outcomes such as quality of life, glucose control, hypoglycemia, and complications. The long term safety of the TrialNet therapies can also be evaluated.

2.1 TrialNet Clinical Trials

TrialNet conducts multiple studies in individuals at risk for disease as well as those post diagnosis.

For Prevention Trials, individuals are currently identified as being at risk through HLA testing or participation in the TrialNet Natural History Study (also known as Pathway to Prevention Study) which screens relatives of individuals with type 1 diabetes for the presence of autoantibodies associated with disease development. Subjects identified through this process are then evaluated and, if eligible, consented for participation in a prevention trial. For example, first or second degree relatives of individuals with type 1 diabetes who are insulin autoantibody (mIAA) and islet cell antibody (ICA) positive, who have normal glucose tolerance but do not have a “protective” HLA type, are eligible for randomization into the TrialNet Oral Insulin Study testing whether daily administration of oral insulin can delay diabetes onset. Antibody positive relatives with abnormal glucose tolerance are at higher risk for development of clinical disease. They may be eligible for enrollment into the TrialNet Teplizumab Prevention study. Relatives who are not eligible for prevention trials, and who have not developed diabetes, are closely monitored for the development of diabetes under the auspices of the TrialNet Natural History Study.

At risk individuals who reach study endpoint (i.e. develop diabetes), who are often diagnosed with diabetes with no symptoms of hyperglycemia, may be eligible for intervention studies for newly diagnosed subjects. If they are not eligible or not interested in such a clinical trial, they would be offered the opportunity to enroll in this long-term follow-up protocol, to follow the natural history of patients so identified. In that they were diagnosed so early in the course of their disease, still often in an asymptomatic state, the remaining course of their disease may differ from individuals diagnosed in the more usual fashion, after clinical symptoms occur, i.e.; at a later point in the disease process.

The long term follow-up of these individuals post-diagnosis may allow for addressing key gaps in our knowledge about the natural history of disease, such as what metabolic and immunologic changes occur around the time of diagnosis and beyond, and the impact of pre-diabetes values to post-diagnosis clinical course. Since prior to diagnosis, insulin secretion has traditionally been measured by response to oral glucose tolerance testing and after diagnosis, by response

to mixed meal tolerance testing; information about both measures may be important during the transition stage from pre to post diagnosis.

For Intervention Trials, after informed consent, eligible individuals with diabetes are randomized to active treatment or control groups. The primary outcome is determined at one or two years after enrollment by evaluation of beta cell function through the C-peptide response to a mixed meal stimulation test (MMTT). As of spring 2011, TrialNet has completed four intervention trials. One, using mycophenalate Mofetil (MMF) with or without Daclizumab (DZB) failed to demonstrate any effect of therapy on preservation of beta cell function as compared to placebo at 2 years. The second, using Rituximab (antiCD20) demonstrated a 20% difference in residual beta cell function (C-peptide) at 1 year after randomization between treatment and placebo groups. The treatment group in this trial also had decreased insulin requirements with better diabetes control (lower HbA1c). A third trial tested the effect of co-stimulation blockade using Abatacept (CTLA4-Ig) and demonstrated a 59% difference in C-peptide between those receiving active drug versus placebo at two years. In this study, there was also better HbA1c, but no effect on insulin dose. The fourth trial tested two or three doses of GAD65 with alum as compared to placebo and no effect of therapy on C-peptide, insulin dose, or glucose control was seen at one year. Two other intervention trials have completed enrollment, but are ongoing with anticipated completion within the next year. Several other intervention trials are planned. Since the Rituximab Trial met its primary endpoint, a study amendment and re-consent of subjects allowing for long-term follow up was implemented but this was not done for the MMF/DZB trial participants. Since the numbers of subjects in any of these intervention trials is relatively small (n~100-150), selective follow-up of only those individuals in trials that met their primary endpoint may limit our ability to interpret the clinical, efficacy, and safety information being collected. This protocol is therefore planned to offer long term follow-up on all subjects who participated in our trials.

3 STUDY DESIGN

3.1 Overview

This is a descriptive study to evaluate the long term effects of participation in TrialNet studies. These include long term effects of either receiving an intervention, or of being diagnosed with diabetes at an early point in the disease process.

The general objectives are to gather descriptive information to address the following:

1. Evaluate the transition between pre-and post-clinical diagnosis with respect to clinical, metabolic, genetic, and immunologic parameters.
2. Evaluate the impact of participation in the Natural History study and /or any interventional trial on the subsequent clinical course post diagnosis.
3. Provide comparison data from a cohort identified prior to diagnosis with those who are diagnosed outside of a research protocol and subsequently enrolled in a clinical trial to preserve beta cell function.
4. Evaluate the long term safety of therapies tested in at-risk individuals who have subsequently developed diabetes.
5. Evaluate the relationship between beta cell function and clinical, metabolic, genetic, and immunologic parameters over time.
6. Evaluate the long term safety of therapies studied in individuals post-diagnosis.
7. Evaluate the long term impact of therapies as compared with control and placebo groups

on clinical, metabolic, genetic, and immunologic parameters.

8. Evaluate the change in diabetes control and beta cell function after completion of clinical trials which include close attention to maintaining glycemic control.

3.2 Summary of Inclusion/Exclusion Criteria

Participants must meet all entry criteria for the protocol as outlined below.

3.2.1 *Inclusion Criteria:*

Potential participants **must meet all** of the following inclusion criteria:

1. Type 1 diabetes
2. Prior participation in TrialNet study.
3. Willing to give, informed consent/assent (as applicable for children).

3.2.2 *Exclusion Criteria:*

Potential participants must not:

1. Be deemed unable or unlikely to comply with the protocol.

4 STUDY ASSESSMENTS

See Appendix 1 and Appendix 2 for detailed scheduled of assessments.

4.1 General Assessments

There are two potential groups of participants:

- Group 1: Prior Participation on TrialNet prevention or TN01 Pathway to Prevention
- Group 2: Prior Participation on any other TrialNet interventional study

Participants can move from semi-annual to annual if they are found to have no residual C-Peptide (on last available Mixed Meal Tolerance Test (MMTT) result) during the study.

4.1.1 *Group 1: Subjects from TN01 Pathway to Prevention or TrialNet prevention studies:*

General assessments for semi-annual visits for this group (Group 1):

-

Subjects will be requested to undergo the following:

- Initial Visit:
  - Oral Glucose Tolerance Test (OGTT)[1]

- 6 Months and 12 Months visits:
  - Oral Glucose Tolerance Test (OGTT)
  - Mixed Meal Tolerance Test (MMTT)

  Note: These tests must be done on separate days, preferably within one week of each other. However, the tests may be conducted any time within visit window. (Refer to Appendix 1)
- Mixed Meal Tolerance Test (MMTT)
  - After 12 Months MMTT will be performed in subjects with detectable C-peptide on last available MMTT.
- Medical History
- Directed Physical Exam
- Concomitant medications
- Adverse event assessment
- Hemoglobin A1C
- Blood or urine tests as needed to follow-up on potential long term safety concerns with a particular therapeutic agent.
- Samples for mechanistic studies related to aim of this protocol as approved by TN study committee

4.1.2 *Group 2: Subjects from all other TrialNet interventional studies:*

Study visits for participants with detectable C-Peptide (at last available result) will occur semi-annually.

Study visits for participants without detectable C-Peptide (at last available result) will occur annually.

General assessments for **semi-annual visits** for this group (Group 2):

- Mixed Meal Tolerance Test (MMTT)
- Medical History
- Directed Physical Exam
- Concomitant medications
- Adverse event assessment
- Hemoglobin A1C
- Blood or urine tests as needed to follow-up on potential long term safety concerns with a particular therapeutic agent
- Samples for mechanistic studies related to aim of this protocol as approved by TN study committee

4.1.3 *Annual Visits - MMTT Result Has No Residual C-Peptide:*

General assessments for **annual visits** for this group:

- Medical History
- Concomitant medications
- Adverse event assessment
- Hemoglobin A1C

- Blood or urine tests as needed to follow-up on potential long-term safety concerns with a particular therapeutic agent.
- Samples for mechanistic studies related to aim of this protocol as approved by TN study committee

4.1.4 *Visit Windows*

- **Group 1**: Initial Visit shall be performed within 2 months +/- 4 weeks of Type 1 Diabetes diagnosis date.
- **Group 2**: Initial Visit shall be performed at any time.
- Semi-Annual Visits: shall be performed within +/- 6 weeks of visit target date
- Annual Visits: shall be performed within +/- 6 weeks of visit target date

Note: Missed Visits or any visits occurring outside of the target window is **not** a deviation. Sites will need to complete the CRF tracking system, indicating that the visit will not be completed.

4.1.5 *Other Study Participation*

- Participation in this study does not preclude participation in other studies.

4.1.6 *Deviations*

Aside from significant consent deviations (no evidence of informed consent being obtained) other deviations will not routinely need to be submitted to the TrialNet Coordinating Center for this protocol. However, sites must comply with local or central IRB guidelines for reporting any deviation of the assessments as stated in this protocol.

4.2 Quality Assurance

During the study, duplicate collections of blood samples for assays will be obtained in a small sample of subjects for the purpose of quality surveillance of the performance of the central laboratories.

5 STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a descriptive study to ascertain the long-term effects of participation in a TrialNet Clinical Trial. Analyses of study data will include the use of data from other studies in combination with data from this study. Likewise, data from this study may be used in combination with data from another study to address objectives of that study.

Cross-sectional studies (e.g. change from baseline at a specific point in time) will employ descriptive statistics, graphs and tests of hypotheses using methods for categorical or continuous data as appropriate. Longitudinal studies (e.g. changes in C-peptide across time) will use plots of proportions for categorical data and longitudinal boxplots or spaghetti plots for continuous data. As specific hypotheses concerning longitudinal behavior arise, generalized linear or non-linear models will be used for both categorical and continuous data. Hypotheses concerning transitions between categories across time (e.g. from “responder” to “non-responder”) will be analyzed with Markov transition models. Analyses by gender and

race/ethnicity, as appropriate, are also planned.

The data we have specified to collect, and the statistical methods we propose, will ensure that subsequent papers will meet the "STROBE" criterion for reporting results from observational research[1]. That is we will assess the potential impact of selection, ascertainment, and loss to follow-up biases on study results by comparing characteristics of subjects who are in this study versus those who have not been included or who are lost to follow-up and by then matching on length of ascertainment. Descriptive summaries and statistical comparisons for two-group comparisons using methods appropriate to either categorical or continuous data and adjusted for covariates will be used as appropriate. In addition, patterns of missing data will be summarized with categorical methods and longitudinal graphs stratified or statistically comparing gender, age, and race/ethnicity and other covariates. Confounding issues (e.g. "Healthy-patient" and "selective prescribing" [2]) in the analysis of safety data will be will also be addressed by including covariates into key statistical analyses.

6 HUMAN SUBJECTS CONSIDERATIONS

6.1 Disclosure of Results to Participants

During the course of the study individual testing results will be disclosed to participants. The disclosures will be performed in a standardized fashion by qualified researchers and will include measures related to diabetes control (e.g. HbA1c and/or glucose monitoring) and insulin secretion.

There will be communications to participants about scientific information that we are gaining from the study as a whole.

6.2 Risks and Benefits

6.2.1 *Risks*

The risks of this study are presented in the informed consent form and are described above.

The physical risks of participation in this protocol are those associated with obtaining a blood sample including venipuncture or other method such as finger or heel stick, and adverse effects arising from ingestion of oral glucose or the "mixed meal" (Boost). Discomfort, bruising and infection can occur with obtaining a blood sample. Some subjects may experience minor and transient symptoms during an OGTT or MMTT (nausea) and may not like the taste.

6.2.2 *Benefits*

There is no guaranteed benefit to subjects for their participation in the study. However, Subjects will receive clinically relevant information reflecting their diabetes control (HbA1c and/or glucose monitoring results). Subjects will be notified if any other measures identify a health concern associated with their prior participation in a TrialNet study. In addition, we will share beta cell function information with the participant. While such information is unlikely to impact clinical care, many individuals with diabetes are eager to know whether they are still making insulin**.** The TrialNet Long-Term Follow-up Study will benefit society through increase

knowledge regarding the natural history and prevention of T1D.

6.3 Inclusion of Children

The study procedures are minimal risk and offer the possibility of benefit by providing clinically relevant information about diabetes control and insulin secretion that participants can share with their health care providers. Further, the data is likely to yield general knowledge about T1D which is of importance for the understanding and amelioration of T1D in children. Assent of children along with consent of the child's parent/ legal guardian will be obtained prior to any study procedures. This research proposal in children is therefore consistent with United States Department of Health and Human Services, Protection of Human Subjects, Subpart D, Section 46.404 (Research involving minimal risk) and with Subpart D 50.51 (Clinical investigations involving minimal risk .

6.4 Pregnancy

In individuals who are known to be pregnant, no blood samples will be obtained in this study (during the pregnancy) as metabolic changes may make data interpretation difficult.

However, as the study procedures pose no increased risk to mother or fetus, if an individual is unknowingly pregnant, pregnancy tests will not be done as part of the study.

7 ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

7.1 Statement of Compliance

This study will be conducted in compliance with the protocol and consistent with current Good Clinical Practices (GCP), adopting the principles of the Declaration of Helsinki, and all applicable regulatory requirements (ICH E6, 45CFR46, and FDA 21CFR sections 11, 50, 56, 312).

Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate Independent Ethics Committee/Research Ethics Board (IEC/REB) or Institutional Review Board (IRB). Any amendments to the protocol or consent materials must also be approved before they are implemented.

7.2 Participating Centers

Participating TrialNet clinical sites must have an appropriate assurance, such as a Federal-wide Assurance (FWA) or an Unaffiliated Investigators Agreement (UIA), with the Office for Human Research Protections (OHRP), since they are actively engaged in research and provide informed consent. The protocol and consent forms will be approved by Institutional Review Boards or Ethics Committee/Research Ethics Boards at each of the participating clinical sites. HIPAA and applicable local regulations will be followed by each participating institution in accordance with each institution's requirements. The participating international sites will obtain approval from their corresponding review boards in accordance with their local procedures and institutional requirements.

The investigator is required to keep accurate records to ensure the conduct of the study is fully documented. The investigator is required to ensure that all case report forms are legibly completed for every participant entered in the trial.

7.3 Informed Consent

The process of assuring that individuals (and parent/guardian if less than 18 years of age) are making an informed decision about participating in this study includes both verbal and written communication.

Informed consent will be administered by TrialNet Study Coordinators or Investigators Potential study participants (and their guardians in the case of minors) will have sufficient time to fully read the consent forms and have any questions answered prior to any study procedures.

An assent form has also been developed for each stage of the study for participants aged 7-17 years (unless local IRB requirements differ in procedure.) Participants within this age range will be given the consent and assent forms 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 otherwise. In addition, the parent(s) or guardian(s) will be given the opportunity to discuss the study apart from the child or adolescent. Individuals in this age group will be re-consented at the first visit they attend after their eighteenth birthday.

All participants will be given a copy of each of their signed consent forms (and assent forms where applicable).

7.4 Study Subject Confidentiality:

The investigational sites participating in this study will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from subjects participating in this study. Subject identifying clinical and research information will be shared between TrialNet sites. Medical and research records will be maintained at each site in the strictest confidence. However, as a part of the quality assurance and legal responsibilities of an investigation, the investigational site must permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress. Unless required by the laws permitting copying of records, only the coded identity associated with documents or other participant data may be copied (obscuring any personally identifying information). Authorized representatives, as noted above, are bound to maintain the strict confidentiality of medical and research information that may be linked to identify individuals. The investigational site will normally be notified in advance of auditing visits. At the end of the study, all records will continue to be kept in a secure location. There are no plans to destroy the records.

Personal information that is obtained for TrialNet will also be maintained in a distinct database at the central TrialNet Coordinating Center (TNCC) at The University of South Florida. All information obtained from this study will be identified with a unique study number, and will not be kept with the participant's name. Data from TrialNet examinations and procedures will be sent to the TNCC. This information will be entered into another database that will be used for statistical analysis. Data from this study will be combined as appropriate with data from other TrialNet studies.

7.5 Sample and Data Storage

Stored samples, including genetic samples, from the study will be kept at a TrialNet Core Laboratory Facility and/or NIDDK Repository Site. The use of these samples will be subject to TrialNet and NIDDK policies and procedures. The samples could be used to learn more about the causes of T1D, its complications, and other conditions for which individuals with diabetes are at increased risk, and how to improve treatment. While TrialNet is active, the use of stored samples will be restricted to TrialNet approved researchers. The samples will be coded with unique study numbers, but TrialNet researchers will be able to identify samples if it is necessary to contact participants to request additional samples, for reasons of health or to notify them about future studies. Researchers from outside of TrialNet will not receive identifying information.

Data collected for this study will be sent to the TNCC. De-identified data will be released to qualified investigators periodically to enhance the scientific utility of this study. After the study is completed, de-identified data will be stored at the NIDDK Repository, under the supervision of the NIDDK/NIH, for use by researchers, including those outside of TrialNet.

When TrialNet is completed, samples will continue to be stored at the NIDDK Repository Sites. Since the stored data will be fully de-identified upon the completion of TrialNet, it will no longer be possible to identify samples. Thus, whereas a sample can be destroyed upon a participant's request during the existence of the TrialNet, it can no longer be destroyed once TrialNet is completed. However, there will still be the potential to link data derived from the samples with data that had been derived from TrialNet studies. Once TrialNet is completed, researchers will only obtain access to samples through proposals approved by the NIDDK. The NIDDK will convene an external panel of experts to review requests for access to samples.

8 ADVERSE EVENT REPORTING AND SAFETY MONITORING

8.1 Adverse Event Definitions

8.1.1 *Adverse Event Reporting*

This long-term follow up study does not involve any intervention. Thus, a reportable adverse event is any occurrence or worsening of an undesirable or unintended sign, symptom or disease **specifically associated with study procedures.**

Throughout the study, the investigator must record adverse events **specifically associated with study procedures on** source documents. Investigators will grade AEs according to CTCAE criteria with the exception of hypo or hyperglycemia. These events will be considered AEs only if associated with need for assistance of others due to altered consciousness or DKA. Those that are deemed as a serious adverse event (SAE) will be recorded electronically (see below for details). The investigator should treat participants with adverse events appropriately and observe them at suitable intervals until the events resolve or stabilize.

Adverse events may be discovered through:

- observation of the participant;
- questioning the participant;

- unsolicited complaint by the participant

In questioning the participant the questioning should be conducted in an objective manner.

8.1.2 *Serious Adverse Event*

For this follow-up study, an adverse event associated with the study procedures that suggest a significant hazard, contraindication, side effect or precaution (as described below) is to be reported as a serious adverse event (SAE).

A serious adverse event (experience) or reaction is any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

8.2 Serious Adverse Event Reporting and Monitoring

For reporting SAEs as defined above, the TNCC should be notified *within 24 hours of when the site was notified of the event.* This will be reviewed by the TrialNet Medical Monitor, the TrialNet Safety Monitoring Committee, and the Data Safety Monitoring Board (DSMB) as appropriate. Participant deaths must be reported immediately. Event outcome and other follow-up information regarding the treatment and resolution of the event will be obtained and reported when available, if not known at the time the event is reported. The follow-up information should contain sufficient detail to allow for a complete medical assessment of the case and an independent determination of possible causality.

9 STUDY ADMINISTRATION

9.1 Organizational Structure

This study is part of Type 1 Diabetes TrialNet which is funded by the National Institutes of Health.

9.2 Groups and Committees

9.2.1 *Long-Term Investigative Follow Up in TrialNet Study Committees*

The Long-Term Investigative Follow-up in TrialNet Committee and TrialNet Executive Committee will receive periodic reports from the TNCC on the progress of the study. These will

include accrual rates and baseline demographic characteristics. Criteria and results of ongoing monitoring of the TrialNet labs in terms of reproducibility will also be provided on a routine basis. As appropriate, abstracts and manuscripts dealing with the progress of the trial shall be directed by the Study Committee.

9.2.2 *TrialNet Chairman's Office and TrialNet Coordinating Center (TNCC)*

The TrialNet Chairman's Office and TNCC will work together in providing leadership to the TrialNet Study Group to include protocol and manual preparation, training for clinical sites, development of statistical design for each study, and analysis of study results. The TNCC will also coordinate interactions among the participating TrialNet clinical centers, test laboratories including TrialNet core laboratories and other subcontract laboratories, NIDDK, and other sponsoring agencies.

9.2.3 *Clinical Site Monitoring*

In order to conduct this study with established research principles, site visits may be conducted during the study to evaluate study conduct. Sites will be monitored by the TNCC and appropriate TrialNet committees for patient enrollment, compliance with protocol procedures, completeness and accuracy of data entered on the case report forms (CRFs), and the occurrence and reporting of AEs and SAEs.

9.2.4 *Medical Monitor and Data Safety and Monitoring Board (DSMB)*

All serious adverse events with the exception of hypo and hyperglycemia as noted above, pertaining to study procedures will be recorded on the adverse event forms, which will be sent to the local IRBs, per their reporting requirements, and to the TNCC.

An independent physician will be designated to serve as the medical monitor for this study who will maintain regular contact with the study and the study chair. (S)he will review all adverse event reports, and will file event reports with regulatory authorities as appropriate.

The DSMB will meet approximately every 3-6 months and as needed to review indicators of safety and study progress. The DSMB will independently evaluate whether there are grounds to modify or discontinue the study.

9.3 Participant Reimbursement and Compensation

Participants will be compensated for each visit attended in the study.

10 References

1. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet.* Oct 20 2007;370(9596):1453-1457.

2. Shrank WH, Patrick AR, Brookhart MA. Healthy User and Related Biases in Observational Studies of Preventive Interventions: A Primer for Physicians. *Journal of General Internal Medicine.* May 2011;26(5):546-550.

APPENDIX 1 - Schedule of Assessment: Semi-Annual Visit Group 1

Prior Participation on TrialNet prevention or Natural History Study and with Residual C-peptide

	Initial[1]		1 YR		2 YR		3 YR		4 YR		5 YR+
Month(s)		06	12	18	24	30	36	42	48	54	60+
Visit Window(s)	+/- 4 weeks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks
Informed Consent	X										
Directed Physical Exam	X	X	X	X	X	X	X	X	X	X	X
Medical History[2]	X	X	X	X	X	X	X	X	X	X	X
Diabetes Management	X	X	X	X	X	X	X	X	X	X	X
OGTT[3]	X	X	X								
MMTT[3,4]		X	X[3]	X[4]	X	X	X	X	X	X	X
HbA1c	X	X	X	X	X	X	X	X	X	X	X
Blood and urine test[5]	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication[2]	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X	X
Mechanistic Specimens[5]	X	X	X	X	X	X	X	X	X	X	X

Evaluations may be conducted with decreased frequency.

1. Initial visit: For those diagnosed with T1DM, initial visit will be 2 months (+/- 4 weeks) from date of diagnosis.
2. Demographics, Medical History (including diabetes management), Con Meds data will be transferred from previous TN trial data. To be confirmed during each visit
3. OGTT and MMTT to be performed at 6 Months and 12 Months visit. These tests must be done on separate days, preferably within one week of each other. However, the tests may be conducted any time within the visit window. For subjects unwilling to come in for two tests at 12 months, the MMTT should be the test performed.
4. After 12 Months, MMTT to be performed only residual C-Peptide is evident at last available MMTT result. In that case, subject transitions to annual monitoring schedule
5. Blood or urine tests as needed to follow-up on potential long term safety concerns with a particular therapeutic agent. Note: subject to be informed about specific test to be done. Samples may also be obtained for mechanistic studies developed to address the aims of this protocol. At no time will blood volume exceed what is allowable per the subject's age and body weight (5cc/kg per day and 9.5cc/kg over an 8-week period for children under age 18, unless otherwise specified by a site's local IRB).

APPENDIX 2 - Schedule of Assessment: Semi-Annual Visit Group 2

Prior Participation in TrialNet Intervention Study and with Residual C-peptide

	Initial		1 YR		2 YR		3 YR		4 YR		5 YR+
Month(s)		06	12	18	24	30	36	42	48	54	60+
Visit Window(s)		+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks	+/- 6wks
Informed Consent	X										
Directed Physical Exam	X	X	X	X	X	X	X	X	X	X	X
Medical History[1]	X	X	X	X	X	X	X	X	X	X	X
Diabetes Management	X	X	X	X	X	X	X	X	X	X	X
MMTT[2]	X	X	X	X	X	X	X	X	X	X	X
HbA1c	X	X	X	X	X	X	X	X	X	X	X
Blood and urine test[3]	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication[1]	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X	X
Mechanistic Specimens[3]	X	X	X	X	X	X	X	X	X	X	X

Evaluations may be conducted with decreased frequency.

1. Demographics, Medical History (including diabetes management), Con Meds data will be transferred from previous TN trial data. To be confirmed during each visit.
2. MMTT to be performed only as long as residual C-Peptide function is evident at last available MMTT result. In that case, subject transitions to annual monitoring schedule (reference Appendix 3 page 23).
3. Blood or urine tests as needed to follow-up on potential long term safety concerns with a particular therapeutic agent. Note: subject to be informed about specific test to be done. Samples may be obtained for mechanistic studies developed to address the aims of this protocol. At no time will blood volume exceed what is allowable per the subject's age and body weight (5 cc/kg per day and 9.5 cc/kg over an 8-week period for children under age 18, unless otherwise specified by a site's local IRB).

APPENDIX 3- Schedule of Assessment: Annual Visits

Prior Participation in TrialNet without C-Peptide

ANNUAL VISITS – GROUP B						
	Initial	**1 YR**	**2 YR**	**3 YR**	**4 YR**	**5 YR+**
Month(s)		**12**	**24**	**36**	**48**	**60+**
Visit Window(s)		**+/- 6wks**	**+/- 6wks**	**+/- 6wks**	**+/- 6wks**	**+/- 6wks**
Informed Consent	X					
Medical History[1]	X	X	X	X	X	X
Diabetes Management	X	X	X	X	X	X
HbA1c	X	X	X	X	X	X
Blood or urine test[2]	X	X	X	X	X	X
Adverse Event Assessment	X	X	X	X	X	X
Mechanistic Specimens[2]	X	X	X	X	X	X

Evaluations may be conducted with decreased frequency.

1. Demographic, Medical History (including diabetes management), Con Meds data will be transferred from previous TN trial data. To be confirmed during each visit.
2. Blood or urine tests as needed to follow-up on potential long term safety concerns with a particular therapeutic agent. Note: subject to be informed about specific test to be done. Samples may be obtained for mechanistic studies developed to address the aims of this protocol. At no time will blood volume exceed what is allowable per the subject's age and body weight (5 cc/kg per day and 9.5 cc/kg over an 8-week period for children under age 18, unless otherwise specified by a site's local IRB).