



Protocol TN01
Pathway to Prevention

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Manual of Operations
Version 2.0 17 July 2014

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1. INTRODUCTION

1.1 Document Description

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

Guideline: A Manual of Operations (MOO) is required for each TrialNet study.

Principles:

- The MOO will be a cooperative work between the Study Chair, Network and the TNCC, with the Study Chair/designee holding responsibility to document proper screening, eligibility determination, and study visit procedures.
- The TNCC will author sections about technical systems and data collection processes.
- The MOO is a fluid document; it can be edited and updated throughout the life of the protocol.
- The TNCC will hold the “master” MOO document, and will post only the latest versions to the TrialNet Web site.
- The MOO must be approved by both the Study Chair/Designee and the TNCC before study initiation.

Process:

The TNCC drafts the initial version of the MOO. TNCC sends to study chair/designee for edits; collaborative development continues between study team and TNCC. When both study team and TNCC are satisfied, they can sign-off (i.e., approve) the current version of the MOO. The sign-off must be in writing or via e-mail.

1.2 Current Protocol Synopsis (15Aug2011)

Title	<i>Natural History/Pathway to Prevention Study of the Development of Type 1 Diabetes</i>
Conducted By	Type 1 Diabetes TrialNet
Protocol Chair	Henry Rodriguez, MD Pediatric Diabetes and Endocrinology University of South Florida 12901 Bruce B. Downs Blvd, MDC62 Tampa, FL 336123 Fax: (813) 974-2580; Email: hrodrig1@health.usf.edu
Study Design	Prospective cohort study
Objective	The overall objective of this study is to perform baseline and repeat assessments over time of metabolic and immunologic status of individuals at risk for type 1 diabetes (T1D) to:(a)

	characterize their risk for developing T1D and identify subjects eligible for prevention trials, (b) describe the pathogenic evolution of T1D, and (c) increase the understanding of the pathogenic factors involved in the development of T1D.
Primary Outcome	The primary outcome is the development of diabetes as defined by the American Diabetes Association (ADA) based on glucose testing, or the presence of symptoms and unequivocal hyperglycemia.
Major Inclusion Criteria	(1) First degree relatives (age 1 – 45 years) of T1D probands. (2) Second and third degree relatives (age 1 – 20 years) of T1D probands: nieces, nephews, aunts, uncles, grandchildren, cousins, half-siblings.

1.3 Study Contacts

TN01 Pathway to Prevention Study TrialNet Coordinating Center (TNCC)		
USF TrialNet Coordinating Center (TNCC) University of South Florida Pediatrics Epidemiology Center Tampa, FL 33615	Primary Contact: Courtney Henderson	Ph.: (813) 396-9541 Fax: 813-910-1246 Email: Courtney.Henderson@epi.usf.edu
	Secondary Contact: Ilma Asif	Ph.: (813) 396-9321 Email: Ilma.Asif@epi.usf.edu

TN01 Pathway to Prevention Study Core Laboratories
Please refer to the Pathway to Prevention Laboratory Manual for a complete list of TrialNet Core laboratories applicable to the TN01 protocol.

For participating site contact information please refer to TN01 Contact Portlet located on the bottom of the protocol homepage of the members website.

Contacts
Study Chair/PI Henry Rodriguez, MD Email Dr. Rodriguez
Coordinator Contacts TN01 Coordinator Contacts
IRB Approved Sites TN01 IRB Approved Sites
TNCC Email Courtney Henderson (Primary CRA) Email Ilma Asif (Secondary CRA) Current USF TrialNet TNCC Contact List

2. STUDY PERSONNEL RESPONSIBILITIES

2.1 *Principal Investigator (Site PI)*

Site PIs are responsible for ensuring the study is conducted in accordance with the protocol, the Code of Federal Regulations, and the ICH Guidelines for Good Clinical Practice (GCP). Specific responsibilities include:

Implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs) at the site to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

Ensure and confirm subject eligibility prior to randomization; reviewing inclusion/exclusion criteria with Study Chair or TNCC on a case-by-case basis, or as needed.

Ensure that all site investigators and research staff are appropriately qualified and fully aware of their obligations.

Ensuring local site initial and continuing Institutional Review Board (IRB)/Ethics Committee review and approval of the protocol (amendments, changes, updates, etc.).

Review local site adverse events (AEs) and ensure that AEs have been addressed appropriately and reported correctly.

Supervise the preparation of training materials and procedure manuals at the site.

Review all trial and patient care issues that occur at the local site.

Monitor protocol compliance at the local site and advise on appropriate response to protocol violations.

2.2 *Trial Coordinator*

The site Trial Coordinators are responsible for coordinating site day-to-day study operations. Specific responsibilities include the following:

1. Recruit potential participants.
2. Screen eligible participants.
3. Participate in enrollment.
4. Administer the consent process.
5. Coordinate participant visits.
6. Utilize and maintain source documents in accordance with the applicable regulations and ICH Guidelines for Good Clinical Practice (GCP).
7. Enter data into electronic case report forms (e-CRFs) within 30 days of participant study visits.
8. Order and maintain study supplies.
9. Respond to data queries / requests for information by the TNCC or Study Chair.
10. Assist in preparation of the initial/continuing IRB submission and drafting study documents.
11. Additional duties as delegated by the PI, as documented on the site delegation log.

2.3 *Role of the TrialNet Coordinating Center*

The TrialNet Coordinator Center (TNCC) was established as part of the TrialNet Study Group to support the overall coordination, data management and analysis of research data for the network.

Specific responsibilities include:

1. Coordinate clinical protocol implementation by assisting with protocol design.
2. Disseminate of information throughout the TrialNet network.
3. Build and maintain data entry forms for data collection and storage.
4. Coordinate laboratory result reporting and sample storage for all samples collected.
5. Assure compliance to applicable regulations and ensure GCP is maintained across all sites.
6. Analyze data in conjunction with the PI and other members of the TrialNet Group
7. Generate reports to assist sites with recruitment, data entry and patient safety
8. Create and maintain updated trainings and protocol manuals for all studies.
9. Create and maintain both the public and members websites for the network.
10. Activate new affiliate sites.
11. Maintain a supply of advertising and incentive materials to aid in the recruitment of participants.

3. STEPS TO SITE ACTIVATION AND ONGOING REGULATORY REQUIREMENTS

3.1 Requirements

Enrollment cannot begin until the site has received an activation letter from the TNCC. The only hard copy document required for activation is the FDA 1572. All other documents required for activation should be sent to the TNCC electronically to regulatory@epi.usf.edu (or by Fax to 813-910-5994).

The following documents need to be submitted to the TNCC prior to activation:

1. Appropriate **IRB/ERB approval** (as below, section 3.2).
2. A current **Site Delegation Log (SDL)** detailing the responsibilities of each staff member as designated by the site PI (as below, section 3.3).
3. **Duality of Interest form(s)** for the PI and the main site coordinator (as below, section 3.4).
4. A completed **New Affiliate Application** consisting of the following forms:
 - a. Site Information Form (SIF)
 - b. Clinical Center Assignment Form
 - c. W9/W8 BEN (W8-BEN is used by non-US sites)
 - d. PHI Sharing Document (not applicable for international sites)
 - e. New User forms for all site members listed on the Site Delegation Log
 - f. Signed and Dated copy of PI's Curriculum Vitae (CV)
 - g. TrialNet Confidentiality Agreement completed by all members listed on the SDL
 - h. All persons listed on the SDL should complete an IRB/ERB approved human subjects education course

In addition to the above documents at least one person at the site must be trained on the online data capture system and be certified for all required study procedures and tests.

3.2 Institutional/Ethics Review Board (IRB/ERB) Approval

Requirements for IRB/ERB Approval:

1. An actual letter or correspondence indicating that the project is approved (with reference to the correct TrialNet protocol title)
2. The date of the approval letter/correspondence
3. IRB/ERB Chair (or chair designee) signature
4. Explicit reference to what the IRB/ERB is approving (the type of submission) and the version date of the protocol and version date of the informed consent (and any additional study documents) to which the IRB/ERB approval/correspondence pertains
5. IRB/ERB approved informed consent(s)/assent(s) indicating the approval and expiry dates. Consents should be stamped or IRB/ERB policy should be provided describing quality control/document version control procedures.

3.3 Site Delegation Log

Requirements of the Site Delegation Log:

1. A separate log must be maintained for each protocol
2. The log must list all persons involved in the conduct of each study and must document the responsibilities delegated to each person by the site Principal Investigator.
3. Each page of the log must contain the PI's signature.
4. The log must include a start and end date (when applicable) for each person listed.
5. The log must be maintained in the regulatory binder
6. If any changes are made to the Site Delegation Log, the PI should initial and date next to all changes made. The updated Site Delegation Log should be submitted to the TNCC once approved by the site PI.

Background:

The TNCC utilizes the Site Delegation Log provided by each site to:

1. Ensure the member directory is current and that study specific correspondence is being sent to all appropriate stakeholders.
2. Ensure each person's permissions in the online system are appropriate.
3. Track site study staff's training by required section or module based on delegated responsibilities.
4. Adherence to 21CFR11.10.

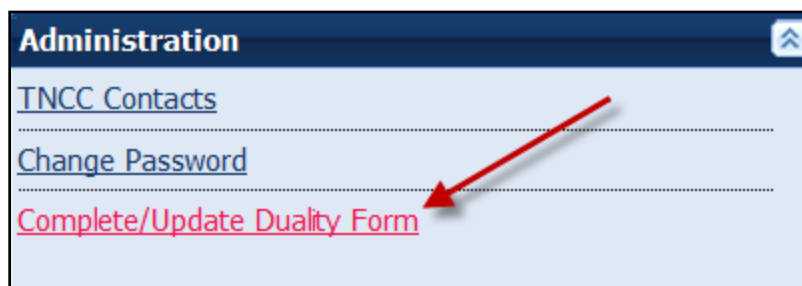
3.4 Duality of Interest Forms

Site activation will require a completed duality of interest form from a minimum of both the PI and main site coordinator.

Each person listed on section 6 of the 1572 must have a duality of interest form on file with the TNCC and it must be updated if there are any changes to a user's information. The duality of interest form must be completed online on the TrialNet members' website. A PDF of the required forms will be emailed to a site prior to study activation upon request.

To access the Duality of Interest form:

- Step 1. From the main TrialNet members' web site, under the Calendar in the "Administration" portlet, click on the link "Complete/Update Duality Form."



- Step 2. The system will display whether any forms have been completed (online) in the last year and provide a link to complete a new DU form or provide an update to the DU form.

The screenshot shows a web interface with a blue header titled 'Duality Of Interest Disclosure Forms - Previous'. Below the header, there is a message: 'No Disclosure of Interest Forms have been completed for this user.' Below this message, there is another blue header titled 'Duality Of Interest Disclosure Forms'. Below this header, there is a link: 'Complete new Duality Of Interest Disclosure Form'.

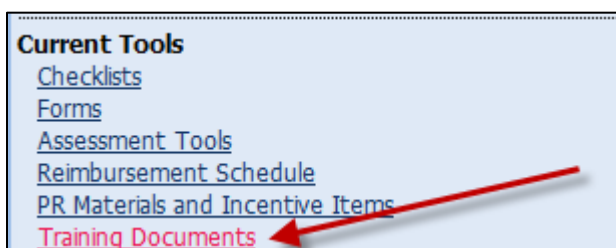
- Step 3. Read and complete the Duality of Interest Disclosure Form. It is important to pay special attention to section 11 – Dualities or revisions by protocol.
- Step 4. Once finished, hit the "save" button. Red text will display beneath the save button indicating that the form has been saved successfully.

The screenshot shows a web interface with three buttons: 'Save', 'Print', and 'Close Window'. Below the buttons, there is a red message: 'Your Duality of Interest form has been saved successfully. Thanks for completing this form!'.

Step 5. Click on the “Close Window” button.

3.5 Study/System Training

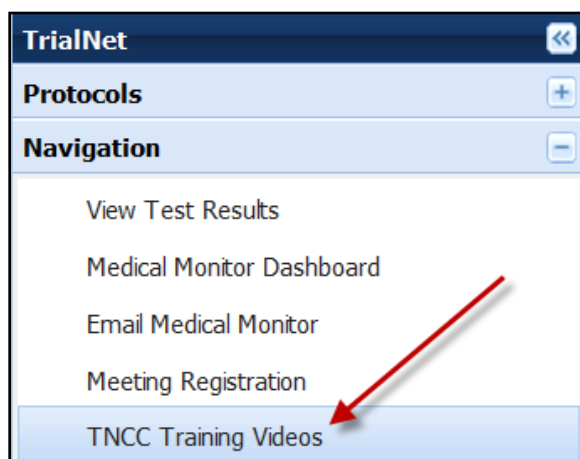
Each site is required to have at least one person trained on the protocol and online system at all times. For a list of current Natural History/Pathway to Prevention Study trainings available, please refer to the Training Matrix in the Training Documents on the TrialNet website TN01-Natural History/Pathway to Prevention Protocol Homepage.



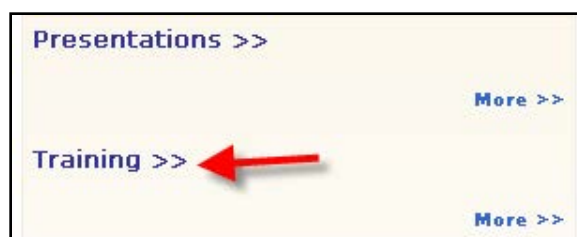
3.5.1 Online Training

Demonstration and training videos are available online. **You must have Windows Media Player** in order to access the videos; they can be viewed at any time by navigating to the online TrialNet media center as follows:

Step 1. From the main TrialNet members' website, on the left side navigation bar, click on the “TNCC Training Videos” link.



Step 2. A new window will open to the media center. Click on the “Training” link.



Step 3. Select the protocol/session of which you would like to view the training.

Training

Note: The training sessions require Microsoft Windows Media Player to view.

To sort by any column, click the column header. Click the header again to invert the sort.

Title
Protocol Training – TN16 Long-Term Investigative Follow Up in TrialNet (LIFT)
TrialNet ADA Affiliate Meeting Presentation
Protocol Training - TN14 Anti IL-1Beta
Protocol Training - TN10 Anti-CD3 Prevention
TrialNet Training – Harmonized Assay Adoption
TrialNet Training - General Members Website
Protocol Training – TN01 Pathway To Prevention
Protocol Training – TN05 Anti CD20
Protocol Training – TN07 Oral Insulin
Protocol Training – TN08 GAD Intervention

Step 4. A list of available videos will display. Select the video you would like to watch.

To sort by any column, click the column header. Click the header again to invert the sort.

Title
TN01 Pathway to Prevention Revised Protocol Training and System Updates
TN01 Natural History "Pathway to Prevention" Study Update
TN01 Pathway to Prevention Study- Screening: Pre-Register a Participant and Labeling Specimen Tubes
TN01 Pathway To Prevention Study- Pathway To Prevention Revised Protocol Training – Screening Only
TN01 Pathway To Prevention Study- Pathway To Prevention Revised Protocol Training – Screening and Monitoring
TN01-Revised Protocol Additional Consent Form Instructions
TrialNet Pathway To Prevention Screening Teleforms – Processing Issues and Proper Form Etiquette
TN01 Teleforms Process

Step 5. Information about the video will display. Select the button “View Presentation for Free.”



Step 6. The video will open in Windows Media Player.

Descriptions of training modules available are as follows:

- 1) TN01 Protocol Overview: Provides a description of the protocol, eligibility criteria, purpose, specific aims, and details of procedures.
- 2) TN01 Online Participant Registration: Provides a guided tutorial of how to register a participant
- 3) GENERAL Members Directory Overview: Provides a non-study specific overview of how to use the online member directory.
- 4) GENERAL Members Website Overview: Provides a non-study specific overview of how to use the online members' website.
- 5) GENERAL Protocol Manager Overview: Provides a non-study specific overview of how to use the online protocol manager page and related sections.
- 6) Harmonized Assay Adoption: reviews TrialNet's adoption of the harmonized assay for GAD65 and IA-2 (ICA512) autoantibody testing and its impact on all current and future studies. Trainings include:
- 7) TN01 Teleforms: explains the procedures for using the teleforms for screenings. This training only applies to sites that use the teleforms for TrialNet Screenings, including initial, rescreen and confirmatory screenings.

3.5.2 Study Certification Quiz

The TN01 Certification Quiz is available online and can be completed by all individuals listed in roles on the Site Delegation Log requiring knowledge of study procedures. Once the certification quiz has been completed the site can request the answers from their clinical center to review.

3.6 Site Activation

The site will receive an email confirmation from the TNCC with their activation letter attached, once the site has fulfilled all of the requirements noted above. The site should retain a copy of the activation letter in their regulatory binder. Once a site receives the activation letter, they may begin enrolling subjects to the study.

3.7 Ongoing Regulatory Requirements

Once activated, a site must maintain current IRB/ERB approval. The study protocol must be reviewed at least annually by a site's IRB/ERB and documentation of an annual review must be

submitted to the TNCC. This regulation applies to all TrialNet sites including international sites. (45CFR46.101 and 45CFR46.103(b)(4)).

Any changes in site staff, site contact information/etc, must be communicated to the TNCC. Below are a few of the more common examples of changes that require reporting to the TNCC:

3.7.1 Addition of New Site Staff

All new site staff must be added to the site's Site Delegation Log (See section 3.2) and a New User Form must be submitted to the TNCC. The new staff user must complete a Duality of Interest form once they are granted access to the online system (See section 3.3).

3.7.2 Removal of site staff

To remove a user, the site should update their Site Delegation Log indicating an end date next to the removed user. Additionally, a Remove User Form should be submitted to the TNCC.

3.7.3 Site Contact Information Changes

For any changes in the name, address, or contact information of a site, please complete a new Site Information Form and submit this to the TNCC. Any users, whose name or contact information has changed, should also complete Contact Change Forms and submit these to the TNCC.

3.7.4 New Primary Site Coordinator

If the primary site coordinator role at a site changes, the site should submit the following to the TNCC:

1. Confidentiality Form for new site coordinator.
2. Documentation of human subjects in research training for new site coordinator.
3. New User Form for new site coordinator (if applicable).
4. An updated SDL with the new primary site coordinator's start date and the previous coordinator's end date.
5. New site coordinator should complete a Duality of Interest form (if not previously completed).
6. If the previous coordinator is no longer at the site, a Remove User form should be submitted (see section 3.8.2).

3.7.5 Changes in Site PI

If the principal investigator changes, the site should submit the following to the TNCC:

1. IRB/ERB modification recognizing the new PI will be continuing the study
2. Confidentiality Form for new PI
3. Documentation of human subjects research training for new PI
4. Signed and dated copy of PI's CV
5. New User Form for new PI (if applicable)

6. Updated Site Delegation Log signed by the new PI.
7. Site should ensure W9/W8 BEN on file at the TNCC still reflects the preferred payment information.
8. New PI should complete a Duality of Interest form (if not previously completed).
9. If the previous PI is no longer at the site, the Site Delegation Log should be updated and a Remove User form should be submitted (see section 3.8.2).

3.7.6 End Participation With TrialNet

If a site no longer wishes to participate in a TrialNet study or no longer has the resources to participate, the following procedures should be completed to officially close a site:

- Step 1. Site should notify their clinical center and the TNCC protocol CRA of their intention to cease participation with TrialNet.
- Step 2. The site should notify their IRB/ERB of the study closure and indicate that all active participants should be transferred to the site's clinical center for follow-up.
- Step 3. The site should submit the IRB/ERB Final Closure documentation and submit the Request to End Participation with TrialNet form to the TNCC.

4. RECRUITMENT PROCEDURES AND STRATEGIES

4.1 Recruitment Goals

A fixed target sample size has not been specified and the date on which the study will terminate has not been fixed in advance. Rather, the study is designed as an *observational trial* in which subjects are recruited and followed until the end of the study. Thus, the exact total sample size and study duration are unknown.

Projected recruitment goal: 15,000 – 20,000 participants screened a year across all sites, with about 5% continuing to the Monitoring stage of the study.

4.2 Recruitment Monitoring

Guidelines:

- The PI delegated, TNCC-trained person(s) at each site will enter enrollment data into the online data capture system.
- All participants who have signed an informed consent document must be registered into the online data capture system (protocol manager).
- Eligibility is confirmed in the online data capture system based on the data entered via the eligibility e-CRF.
- Recruitment reports (by study and by site) will be available at all times online and will be updated monthly (or more often if determined by the study chair).
- Recruitment reports will, at the least, detail
 - By site: total number of Participants registered
- Recruitment reports and efforts will be monitored by the TNCC, study chair, and discussed by the study committee

4.3 Eligibility Criteria

Inclusion Criteria:

The participant MUST:

1. Be willing to give informed consent for screening.
2. Be aged 1 to 45 years, inclusive, and a sibling, offspring, or parent of an individual with T1D.*
3. Be aged 1 to 20 years, inclusive, and a niece, nephew, aunt, uncle, grandchild, cousin, or half sibling of an individual with T1D.*

****In general, a proband with T1D is an individual with onset of diabetes before age 40 years and prescription of insulin therapy within one year of diagnosis. Those who are considered to have T1D but who do not meet this definition will be referred to the TrialNet Eligibility Committee for a decision regarding eligibility.***

Exclusion Criteria:

The participant is not eligible if:

1. Have previous or current use of medications for the control of hyperglycemia (e.g. insulin, oral hypoglycemic agents, including sulfonylureas, metformin, thiazolidinediones, alpha-glucosidase inhibitors, meglitinides, GLP-1 mimetics and DPP4 inhibitors).
2. Currently use immunosuppressive or immunomodulatory therapies, including pharmacologic doses of systemic steroids.
3. Have diabetes by 2011 ADA criteria.
4. Have known severe active diseases, and/or diseases which are likely to limit life expectancy or lead to the use of immunosuppressive or immunomodulatory therapies during the course of the study.
5. Be deemed unable or unlikely to comply with the protocol.

The current ADA criteria for diagnosing diabetes include the following:

1. Fasting (no caloric intake for at least 8 hours) plasma glucose is ≥ 126 mg/dL (7.0 mmol/L)
OR
2. Diabetes symptoms (i.e. polyuria, polydipsia, polyphagia, and/or weight loss) exist and casual (any time of day without regard to time since last meal) plasma glucose is ≥ 200 mg/dL (11.1 mmol/L)
OR
3. 2-hour plasma glucose is ≥ 200 mg/dL (11.1 mmol/L) during a 75 gram oral glucose tolerance test (OGTT)
OR
4. Unequivocal hyperglycemia with acute metabolic decompensation (e.g. ketoacidosis)

The first three criteria in any combination on two separate days are diagnostic. If criterion (4) is met, an OGTT is not recommended.

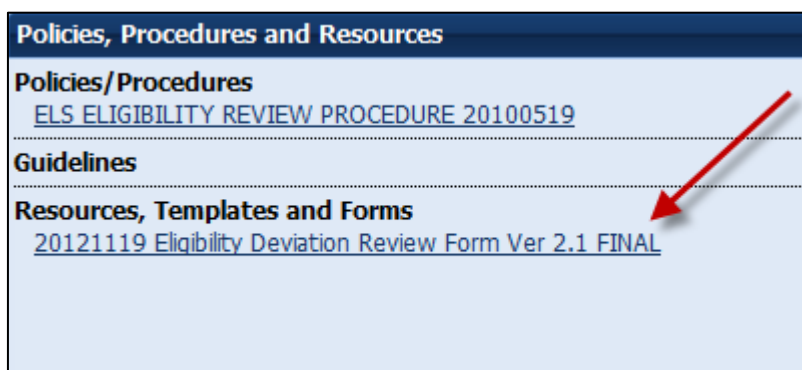
4.4 Exceptions to Questions Regarding Eligibility Criteria

The TrialNet Coordinating Center will be responsible for initially reviewing and adjudicating any instances where eligibility is unclear. If following this initial review eligibility is still unclear, the TrialNet Eligibility Committee will review and adjudicate the situation.

4.4.1 Procedures for submission to the TrialNet Eligibility Committee

Prior to the submission, the study coordinator should do the following:

- Step 1. Contact the TNCC CRA to review the question or matter regarding eligibility if unclear in the protocol
- Step 2. If TNCC CRA unable to clarify proceed to complete the Eligibility Deviation Review Form. This form is located in the Eligibility Subcommittee page under the Policies, Procedures and Resources Portlet.



- Step 3. Complete all portions of this form except the section titled "TNCC Only" and email back to the lead TNCC CRA and cc Julie Ford.
- Step 4. Once a decision has been made by the Eligibility Deviation Review Committee a copy will be provided to the site. It should be initialed, dated and placed with your source documents.

		Eligibility and Deviation Review Form Complete all highlighted sections		08Dec2009 Version 2.0 Page 1 of 1
Participant ID:		Local Code:		FTL:
		Study: TN 0	Study Name: Select	
A. GENERAL INFORMATION 1. Date of review request: (MM/DD/YYYY) 2. Date response needed by: (MM/DD/YYYY)		Provide dates as indicated and complete this section.		
B. GENERAL SUBJECT INFORMATION 1. Age (years): 2. Sex: 3. Date of diagnosis with type 1 diabetes (if applicable): (MM/DD/YYYY) 4. Date of screening visit (if applicable): (MM/DD/YYYY)		Complete this section & answer all questions		
		<input type="radio"/> Male <input checked="" type="radio"/> Female		
C. ELIGIBILITY ISSUE DETAILS 1. Provide a brief description of the eligibility issue/deviation that requires review: <div style="background-color: #e6f2ff; padding: 10px; margin-top: 5px;"> Note: In the description include dates if applicable i.e. visit timepoint & visit timepoint dates. </div>				
2. Provide a brief justification for the subject's enrollment into the study: <div style="background-color: #e6f2ff; height: 60px; margin-top: 5px;"></div>				
D. RELEVANT INFORMATION FROM STUDY DOCUMENTS <div style="background-color: #e6f2ff; height: 60px; margin-top: 5px;"></div>				
TNCC USE ONLY				
1. Eligibility reviewed? IF YES,		Sites should not complete this section only TNCC		
a. Date of review:				
b. Reviewer		<input type="checkbox"/> TNCC <input type="checkbox"/> Committee Chair <input type="checkbox"/> Full Committee		
c. Eligibility decision:		<input type="checkbox"/> Eligible <input type="checkbox"/> Not Eligible		
IF NO, a. Reason not reviewed:				
2. Comments:				

4.5 Follow-up of Eligible Study Participant

Once a participant has been asked to participate in this study please complete the Follow Up of Eligible Study Participant eCRF. *(Please Note: For the corresponding assessment tool please see section 5.)*

This form should be completed for all participants that are asked to participate regardless of whether they decline or agree to participation in the study.

Step 1: Please select the form located under PRN forms in their **TN01** Participant Details page.

Additional Study Forms / Events

-- Select --

-- Select --

- Additional Consent
- Additional Site Comments
- Autoantibody Positive Follow-up
- Change of Monitoring Schedule
- Follow-up of Eligible Prevention Study Participant
- NH05 - Follow-Up Risk Assessment
- NH05C - Follow-Up Risk Assessment
- NH07 - Change of Status
- NH08 - Diabetes Onset
- NH09 - Follow-Up Missed Visit
- NH13 - Protocol Deviation/Procedural Error
- NH20 - Permanent Participant Site Transfer
- Pathway to Prevention Visit Assignment Form
- Physician/Lab Reimbursement Form
- Report new Adverse Event

Step 2: Please ensure that all parts of the form are completed. If the participant chooses to screen for the study please select “yes” for question 4. There is no need to complete sections 4a or 4b.

4. Is the participant interested in participating in the above study?

☐ Yes ☐ No ☐ Not Sure

If the participant declines to screen for the study please select “no” for question 4. Sections 4a and 4b should be completed. For section 4a please check all reasons the participant states for not wanting to participate in this study. *(Please Note: more than 1 reason can be checked.)*

4a. If responding "No" or "Not Sure", please indicate the reason(s) the participant is not currently interested in the study? (Check all that apply)

Reasons	Please rank the importance of this reason for the participant declining the study
<input type="checkbox"/> Conflicting Responsibilities (Work, School, Family)	<input type="radio"/> 1 Very Important <input type="radio"/> 2 Important <input type="radio"/> 3 Somewhat Important
<input type="checkbox"/> Time Commitment	<input type="radio"/> 1 Very Important <input type="radio"/> 2 Important <input type="radio"/> 3 Somewhat Important
<input type="checkbox"/> 2 week Infusion Period	<input type="radio"/> 1 Very Important <input type="radio"/> 2 Important <input type="radio"/> 3 Somewhat Important
<input type="checkbox"/> Unable/ Unwilling to Travel	<input type="radio"/> 1 Very Important <input type="radio"/> 2 Important <input type="radio"/> 3 Somewhat Important
<input type="checkbox"/> Participant does not tolerate OGTT/IVGTTs well	<input type="radio"/> 1 Very Important <input type="radio"/> 2 Important <input type="radio"/> 3 Somewhat Important
<input type="checkbox"/> Fear of Study Drug Risks	<input type="radio"/> 1 Very Important <input type="radio"/> 2 Important <input type="radio"/> 3 Somewhat Important
<input type="checkbox"/> Concerns about receiving placebo	<input type="radio"/> 1 Very Important <input type="radio"/> 2 Important <input type="radio"/> 3 Somewhat Important
<input type="checkbox"/> Family wishes to wait until participant is older	<input type="radio"/> 1 Very Important <input type="radio"/> 2 Important <input type="radio"/> 3 Somewhat Important
<input type="checkbox"/> Does not want to be blinded to individual test results during the study	<input type="radio"/> 1 Very Important <input type="radio"/> 2 Important <input type="radio"/> 3 Somewhat Important
<input type="checkbox"/> Unwilling to take investigational drug	<input type="radio"/> 1 Very Important <input type="radio"/> 2 Important <input type="radio"/> 3 Somewhat Important
<input type="checkbox"/> Pregnant, nursing or planning children in the future	<input type="radio"/> 1 Very Important <input type="radio"/> 2 Important <input type="radio"/> 3 Somewhat Important
<input type="checkbox"/> Monetary Compensation	<input type="radio"/> 1 Very Important <input type="radio"/> 2 Important <input type="radio"/> 3 Somewhat Important
<input type="checkbox"/> Other	<input type="radio"/> 1 Very Important <input type="radio"/> 2 Important <input type="radio"/> 3 Somewhat Important
<input type="checkbox"/> Refused; no reason given	<input type="radio"/> 1 Very Important <input type="radio"/> 2 Important <input type="radio"/> 3 Somewhat Important

If other, specify:

Step 3: Please ensure the completed assessment tool is located in the participant's binder.

A new form should be completed whenever a participant's information changes or they become eligible for a different study. For example, if the reason(s) why a participant is declining the study change, then a new form should be completed.

5. VISIT PROCEDURES

The source documents for all visits are located on the members website in the TN01 Protocol Area:

1. Go to the portlet entitled "Working Documents"
2. Scroll down to subsection entitled "Current Tools"
3. Scroll down and select the link entitled "Assessment Tools."

For laboratory collection, labeling, packing, and shipping instructions please refer to the TN01 laboratory Manual of Operations.

5.1 Initial Screening

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Order any supplies needed for the study procedures through the online Fisher BioServices Supply Ordering System. See section 6.4 for a list of supplies required for each specimen collection.	NA	NA
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc). Refer to instructions above for location of visit checklists.	NA	NA
At Visit	Administer the screening consent and if applicable screening assent, and local HIPAA form.	Consent & Assent	NA
At Visit	Register the participant in the online system	NA	Participant Registration Form; Screening Visit Start Date & Pathway to Prevention Visit Assignment Form, Screening Form
At Visit	Collect participant's family history	Family History Form	Family History Form
At Visit	Ask the participant about what medications he/she is currently taking.	NA	NA
At Visit	Screening lab collection: <ul style="list-style-type: none"> Serum - Autoantibodies 	Signed and dated printout of specimen collection form	Screening Specimen Collection
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.2 Confirmatory/Rescreening

Window: Within 1 Year of Initial Screening +/- 3 Months

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, etc).	NA	NA
At Visit	. Administer consent (and assent if participant is under the age of 18), if applicable	Consent	NA
At Visit	Ask the participant about what medications he/she is currently taking.	NA	NA
At Visit	Screening lab collection: <ul style="list-style-type: none"> Serum - Autoantibodies 	Signed and dated printout of specimen collection form	Autoantibodies Specimen (Confirmatory) for Confirmatory; Annual Rescreen Specimen Collection (if within visit window); PRN Autoantibodies (Rescreen) (if outside visit window)
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the SMS Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.3 Baseline Monitoring

Window: Within 1 Year from Screening (if 2+ Ab positive) or Confirmatory (if 1 Ab positive)

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, etc).	NA	NA
At Visit	Administer Monitoring Consent (and Assent, if applicable)	NA	Pathway to Prevention Visit Assignment; Baseline Monitoring Start Date
At Visit	Collect participant's medical history and assess any Adverse Events.	Baseline Monitoring Visit Form	Baseline Monitoring Risk Assessment
At Visit	Ask the participant about any changes in medication since last visit	NA	NA
At Visit	Conduct a limited physical exam	Baseline Monitoring Visit Form	Baseline Monitoring Risk Assessment
At Visit	Conduct a Urine Pregnancy Test (if applicable)	NA	NA
At Visit	Visit lab collection: <ul style="list-style-type: none"> OGTT Serum – Autoantibodies Whole Blood – HbA1c HLA Mechanistic Samples (if applicable) 	Signed and dated printout of specimen collection form	Baseline Specimen Collection
At Visit	Administer Lifestyle Questionnaire	Lifestyle Questionnaire	NA
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s).	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.4 Annual Monitoring

Window: 1 Year (+/- 3 Months)

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, etc).	NA	NA
At Visit	Collect participant's interim medical history and assess any Adverse Events.	Annual Follow-Up Monitoring Form	Follow-Up Risk Assessment Form
At Visit	Ask the participant about any changes in medication since last visit	NA	NA
At Visit	Conduct a limited physical exam	Annual Follow-Up Monitoring Form	Follow-Up Risk Assessment Form
At Visit	Conduct a Urine Pregnancy Test (if applicable)	NA	NA
At Visit	Visit lab collection: <ul style="list-style-type: none"> Serum – Autoantibodies Whole Blood – HbA1c <i>Mechanistic Samples, if applicable</i>	Signed and dated printout of specimen collection form	_ Year Specimen Collection
At Visit	Administer Lifestyle Questionnaire	Lifestyle Questionnaire	NA
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s).	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.5 Semi-Annual Monitoring

Window: 6 Months (+/- 6 Weeks)

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, etc).	NA	NA
At Visit	Collect participant's interim medical history and assess any Adverse Events	Semi-Annual Monitoring Follow-Up Form	Follow-Up Risk Assessment Form
At Visit	Ask the participant about any changes in medication since last visit	NA	NA
At Visit	Conduct a limited physical exam (at semi-annual visit time points)	Semi-Annual Monitoring Follow-Up Form	Follow-Up Risk Assessment Form
At Visit	Conduct a Urine Pregnancy Test (if applicable)	NA	NA
At Visit	Visit lab collection: <ul style="list-style-type: none"> OGTT Serum - Autoantibodies Whole Blood – HbA1c <i>Mechanistic Samples, if applicable</i>	Signed and dated printout of specimen collection form	X Year Specimen Collection
At Visit	Administer Lifestyle Questionnaire (at annual time points)	NA	NA
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s).	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.6 Description of Study Procedures

5.6.1 Pregnancy Monitoring (if applicable)

Females:

Urine pregnancy tests should be performed for women of child bearing potential, if required by local ethics review board. If performed, the test results should be noted on the source document.

If a participant is determined to be pregnant during the course of the study then the site should do the following:

- Step 1. Instruct the participant that monitoring of diabetes risk and pregnancy should be continued by her OB/GYN because she will not be monitored by the Pathway to Prevention study while pregnant.
- Step 2. Ask the participant if they would be willing to provide pregnancy outcome data, and if she is willing to return for scheduled visits after pregnancy outcome. If the participant agrees, the coordinator should instruct them to call the site upon outcome of pregnancy to provide this data.
- Step 3. Complete an NH07 Change in Status e-CRF in the online data capturing system and indicate the participant is discontinuing because of pregnancy.
 - A. If the participant is willing to continue with future follow-up visits after the pregnancy, please indicate this in question 3.
 - B. The reason for withdrawal would be “pregnancy”
- Step 4. Fulfill any local reporting requirements (IRB, GCRC, etc.).
- Step 5. Contact the TN01 Protocol CRA at the TNCC for additional questions or concerns.

Participants are not eligible for Monitoring study visits while pregnant.

Participants are eligible to continue with study visits 3 months after the outcome of the pregnancy. If a participant who was previously pregnant would like to return for continued follow-up, the site should complete an NH07 Change in Status e-CRF to reactivate the participant and continue follow-up based on the participant’s original visit schedule.

5.6.2 Former DPT-1 Participants

Former DPT-1 participants who are eligible begin their participation in Follow Up Monitoring, not Screening or Baseline Monitoring. These participants are followed as a separate subgroup and are not given a full risk assessment.

For this distinct subgroup, the risk assessment time period actually started when they were screened in DPT-1. Therefore, re-assessing them would be akin to resetting the clock and ignoring all the time that elapsed prior to doing the Baseline Risk assessment.

Since the risk assessment will not be reassessed from DPT-1, all former DPT-1 participants will continue to follow the semi-annual visit schedule followed during the DPT-1 protocol. OGTT results on the “View Test Results” page for each former DPT-1 participant will show the C peptide and insulin, as well as the glucose results for each timepoint collected.

5.7 End of Study Participation

5.7.1 Participant Registered in Error

If it is determined that a site has registered a participant in error it is important to contact the TNCC. The TNCC will remove the erroneous entry from the online data capture system.

5.7.2 Participant Withdrawal or Lost to Follow-up

If it is determined that a participant has withdrawn or has been lost to follow up, the site should complete the NH07 Change in Status e-CRF in the online EDC system.

1. The "Date change in status become effective" should reflect the date the participant withdrew or the date it was determined the participant was lost to follow up.
2. Proceed to section B, enter a date of withdrawal if appropriate and indicate the primary reason for withdrawal.
3. No further e-CRFs or visits will be expected in the system for the participant.

If later the participant resumes participation on the trial the site should complete the NH07 Change in Status e-CRF in the online EDC system and indicate the participant has rejoined the study.

1. The "Date change in status become effective" should reflect the date it was determined the participant rejoined the study
2. Proceed to section C, enter the date of the participant's first visit rejoining the study
3. The participant will rejoin the study according to the time point at which they would currently be if they had remained on the study (for example, if the participant left the study at month 3 and rejoined the study 15 months later, the next expected visit- and therefore procedures to follow- would be the 18 month visit).

5.7.3 Participant – Determining Lost to Follow Up

In determining if participant is Lost to Follow Up, the site coordinator should do the following:

1. Contact the participant by phone, email, or regular mail.
2. Note date and how participant is contacted in the source document.
3. If no response after third try, send a certified letter to the participant.
4. If still no response after the certified letter was sent, review with PI and deem participant "Lost to Follow Up."
5. If deemed as Lost to Follow Up, complete an NH07 Change in Status e-CRF.

5.7.4 Participant- Natural End of Study (all visits completed)

The TNCC will provide an end of study report to all sites. Once this report becomes available the site should schedule all participants for a final visit to provide each participant with the report and answer any questions they may have.

Note: No e-CRF's need to be completed for this visit.

5.7.5 Onset of Diabetes

Criteria for diabetes onset are, as defined by the American Diabetes Association (ADA), based on glucose testing, or the presence of unequivocal hyperglycemia with acute metabolic

decompensation (diabetic ketoacidosis). One of the following criteria must be met on two occasions as soon as possible but no less than one day apart for diabetes to be defined:

1. Symptoms of hyperglycemia and a casual plasma glucose ≥ 200 mg/dL (11.1 mmol/L). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss.

OR

2. Fasting plasma glucose (FPG) ≥ 126 mg/dL (7 mmol/L), fasting is defined as no caloric intake for at least 8 hours.

OR

3. 2-hour plasma glucose (PG) ≥ 200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 1.75 g/kg body weight to a maximum of 75 g anhydrous glucose dissolved in water.

It is preferred that OGTTs for diagnosis are analyzed using TrialNet laboratories.

If a participant has an OGTT that indicates diabetes (clinical alert), the site should invite the participant for a repeat OGTT within 60 days. In order to make a diagnosis of diabetes, each of two consecutive OGTTs must meet diabetes criteria. Thus, if the second OGTT does not confirm the diagnosis, the participant will continue to be followed in the Pathway to Prevention Study and will be asked to return for the next follow-up visit. At that time, the OGTT will be repeated and, if indicative of diabetes, will need to be performed a second time to confirm the diagnosis.

There are two settings in which a complete OGTT is not recommended. These are:

1. unequivocal hyperglycemia with acute metabolic decompensation (diabetic ketoacidosis)

AND/OR

2. The fasting glucose is found to be ≥ 250 mg/dL (13.8 mmol/L).

If a participant is diagnosed with T1DM, the site should follow these procedures:

1. Complete the NH07 Change in Status e-CRF PRN in the online electronic data capture system and indicate that the subject has developed Type 1 Diabetes and is inactive.
 - a. The "Date change in status became effective" should reflect the date the participant was diagnosed with type 1 diabetes.
 - b. Proceed to section B, enter a date of withdrawal and indicate the primary reason for withdrawal (development of T1D).
2. Complete the NH08 Diabetes Onset Form in the online electronic data capture system and indicate the participant has developed diabetes.
3. Complete the Follow-Up of Eligible Participant form in the online electronic data capture system and indicate whether or not the subject is interested in participating in another TrialNet study if eligible.

The date of diagnosis will be defined as follows:

1. If the participant was symptomatic at diagnosis, the date of diagnosis will be the date of the **first** OGTT.
2. If the participant did not have symptoms at diagnosis, the date of diagnosis will be the date of the second (or confirmatory) OGTT.

Special Circumstances: Certain situations will arise that will require special procedures in order to make a diagnosis of diabetes. These procedures are based on the following guiding principles:

- a) It is *strongly preferred* that at least one of the required diagnostic OGTTs be performed at a TrialNet Center or Affiliate and that the samples for plasma glucose, C-peptide and insulin levels be sent to the TrialNet Beta-Cell Function Laboratory.
- b) For testing that cannot be done at a TrialNet Center or Affiliate, it is *strongly preferred* that the samples be collected and sent to the TrialNet Beta-Cell Function Laboratory for plasma glucose levels rather than relying on test results from the local (non-TrialNet) lab.
- c) The judgment about whether to perform an OGTT when there is concern that it will affect the participant's safety should be made by the Center Director or Affiliate physician. [NOTE: All participants with fasting glucose levels ≥ 126 mg/dL (7.0 mmol/L) should be evaluated for the presence of symptoms and ketones prior to performing the OGTT.]

For cases in which the results of tests and/or the test procedures are uncertain (e.g., plasma glucose levels performed at a local lab), will be provided to the TNCC for review and adjudication by the TrialNet Eligibility Committee.

Scenario 1:

A participant is scheduled for a routine OGTT at a TrialNet Center or Affiliate but the full OGTT is not completed (e.g., only a fasting plasma glucose is collected according to criterion (c) above, or other circumstances make it impossible to complete the full test

Recommended Action: All collected samples for glucose, insulin and C-peptide should be forwarded to the TrialNet Laboratory. The site should select "not collected" for any samples that were not collected and document the reason in their source documents. If this was to be the initial rather than confirmatory OGTT, the participant should be asked to return for a full OGTT.

The rescheduled OGTT would be considered a confirmatory OGTT if the prior fasting glucose level was ≥ 126 mg/dL otherwise this test would be considered a substitute for the failed OGTT. The participant should return for this test as soon as possible at the Center or Affiliate. If the participant cannot return for the repeat testing at a TrialNet site, follow instructions in scenario 2 below.

NOTE: The participant should be told to contact his/her physician immediately if symptoms of hyperglycemia occur in the interim prior to the next scheduled TrialNet study visit.

Scenario 2:

The OGTT performed at a routine visit, meets the diagnostic criteria for diabetes (with no metabolic decompensation) and the participant is unable to return to the Center or Affiliate for a repeat OGTT.

Recommended Action: Follow the steps outlined in section 6.5 regarding the completion of visit procedures at an unapproved site.

Scenario 3:

A blood glucose sample is obtained locally which meets diagnostic criteria without evidence of metabolic decompensation, and the participant has not already had an OGTT at a Center or Affiliate that is diagnostic for diabetes.

Recommended Action: The participant should obtain a copy of the local test result and contact the physician or study coordinator at his/her TrialNet Clinical Center or Affiliate. The participant should return to a TrialNet site for an OGTT that includes C-peptide and insulin samples within 60 days. If the glucose results are in the diagnostic range, diabetes is confirmed (subject to review by the EEC).

If the participant cannot return to a TrialNet site for confirmatory OGTT testing, please follow instructions in scenario 2.

Scenario 4:

A participant has symptoms of metabolic decompensation and is seen by a local physician in an office or hospital setting.

Recommended Action: The participant will have a plasma glucose measurement, and other lab values, obtained immediately. If the glucose level meets diagnostic criteria for diabetes, and the participant is symptomatic, the participant's physician will determine how to proceed clinically. The Clinical Center (or Affiliate) should obtain all relevant test results pertaining to a diagnosis of diabetes from the participant. Additional lab results relevant to a possible diagnosis of ketoacidosis (serum electrolytes including bicarbonate level, serum ketone levels, urine ketone levels) also need to be obtained if available. This information should be forwarded to the TNCC for subsequent review by the EEC.

Scenario 5:

A participant has elevated blood glucose results upon self-monitoring.

The Natural History Trial does not require routine self-monitoring of blood glucose; however, it is possible that research participants will detect elevated blood glucose values based on home blood glucose testing as many participants have a family member with type 1 diabetes who tests regularly.

Recommended Action: The participant should be asked to return to the TrialNet Clinical Center or Affiliate for a complete OGTT as soon as possible. A participant who is unwilling or unable to travel for the test may have an OGTT completed at an unapproved site. Follow instructions outlined in scenario 2.

If a confirmatory specimen was sent to the TrialNet lab and either the fasting or 2 hour plasma glucose as obtained by an OGTT are in the diabetic range, a diagnosis of diabetes can be made. If only local results are available, the diagnosis will be made subject to review by the EEC.

Scheduling Confirmatory OGTTs:

When a participant has an OGTT result that indicates diabetes (clinical alert), the site will receive an email notification from the TNCC and lab stating "Repeat OGTT requested. Follow

your study procedures for the next action to take or contact your TNCC Clinical Research Administrator.” The site should contact the participant to schedule a confirmatory OGTT as soon as possible and no more than 60 days after the first clinical alert OGTT was collected.

A request to repeat the OGTT should not be interpreted as a diagnosis of diabetes when asking subjects to schedule a confirmatory test. It is important to explain to subjects that these findings need to be confirmed before making a diagnosis of diabetes. In addition to temporary metabolic fluctuations due to illness or stress, there may be other reasons why an OGTT may need to be repeated (e.g. laboratory error, degradation of sample, shipping problems, etc.).

When the confirmatory OGTT is performed outside of a scheduled visit, the site should use a PRN OGTT Specimen Collection Form located in the PRN Collection drop down menu. Please refer to section 9.6.4 for accessing PRN collection forms in the online data capture system.

If the repeat OGTT indicates diabetes, the site will receive a second alert via email from the TNCC and the lab. At this time, the participant has met criteria for a diagnosis of diabetes (and has met study endpoint). Sites should complete the procedures outlined above (complete NH07 and NH08 forms). Coordinators should contact the TNCC Clinical Research Administrator if they have any questions.

5.7.6 Death

All deaths are considered serious adverse events and should be reported within 24 hours of notification, as this is an unexpected event for participants in the Pathway to Prevention Study. Site coordinators should follow these procedures:

1. Report an adverse event for the incident within 24 hours of notification.
2. Complete an NH07 Change in Status form in the online data capture system indicating the participant is becoming inactive.
 - a. The reason for change in status to inactive would be “death”
3. Send a copy of the death certificate (if/when available) to the TNCC.

5.8 Missed Visits/Visits Occurring Outside Window

5.8.1 Missed Visit

If a visit is missed the site should do the following:

1. For that visit time point, under “Tracking” select “Not Done” for all forms and indicate the reason the visit was not completed within the allowable window.
2. Complete an NH09 Follow Up Missed Visit form in the online data capture system indicating the participant missed a visit.
3. Document the reason for the missed visit in the source.

Note: A protocol deviation does not need to be completed for a missed visit for the Pathway to Prevention study.

5.8.2 Visit Occurs Outside of Allowed Window

If a visit is completed outside of the allowable visit windows the site should do the following:

1. Complete the visit e-CRF's using additional study forms (PRN forms).
2. For that visit time point, under "Tracking" select "Not Done" for all forms and indicate the reason the visit was not completed within the allowable window.

Note: A protocol deviation does not need to be completed for a visit that occurred outside of window for the Pathway to Prevention study.

5.8.3 Missed or Incomplete Specimen Collections

When scheduling specimen collections during visits, Study Coordinators should keep in mind the prioritization of samples; refer to the TN01 Blood Volume Table and Individual Assay Plan.

If a sample is not collected during a scheduled visit, Study Coordinators should proceed as follows:

- Step 1. If the missed sample is used to determine study endpoint (such as an OGTT), the participant should be scheduled to return for the procedure as soon as possible.
- Step 2. If the missed sample is not used to determine study endpoint (i.e. autoantibodies, HbA1c, PBMC/Plasma, and RNA) the study coordinators should attempt to reschedule the participant. Although strongly encouraged, rescheduling these types of missed collections is not as imperative as rescheduling study endpoint collections.
- Step 3. Completion of forms:
 - a. If the participant returns for the collection and it occurs within the allowable visit window for that visit then the site should:
 - i. Collect the specimen using the collection form listed under that visit in the participant details page (and not a PRN form, also no protocol deviation).
 - b. If the participant returns for the collection and it occurs outside of the allowable visits window, the site should:
 - i. Collect the specimen using a PRN form.
 - ii. In the specimen collection form for the actual visit, indicate "Not Collected" for the missed sample.
 - c. If the participant does not return for the collection at all, then the Study Coordinator should:
 - i. In the specimen collection form for the actual visits, indicate "Not Collected" for each sample missed during the scheduled visit.
 - ii. Complete a protocol deviation e-CRF in the online data capture system indicating "Baseline procedure/blood collection required by protocol not completed."

5.8.4 Tracking Completion

When a procedure for a study visit is not complete or is completed outside of the allowable visit window, "Tracking" should be completed in the online data capture system for that procedure.

To complete tracking, study coordinators should proceed as follows:

- Step 1. Navigate to the missed procedure in the participant's details page (e.g. If 1 year specimens were not collected).
- Step 2. Select "Tracking" next to the procedure form.

1 year	1 Year Specimen Collection	Tracking
--------	--	--------------------------

- Step 3. Select "Not Done" and select or indicate the reason the procedure was not completed during the scheduled visit window. Then select "Submit."

Event Tracking Form

Event name: **1 Year Specimen Collection**
Time point: **1 year**

* These fields are required in order to SAVE the form

Event done? *
☐ Not Done

Why wasn't this done? *

☐ Participant missed appointment
☐ Participant/parent refused
☐ Unable to obtain sample
☐ Unable to contact subject
☐ Illness
☐ Other

5.8.5 Sample Destruction

If a participant determines that they do not want their samples stored, whether during enrollment or the course of the study, the TrialNet Coordinating Center (TNCC) is responsible for notifying the laboratories of the participant's request and ensuring it has been successfully completed. Upon notification of sample destruction, the laboratories will destroy any participant samples in storage and no further samples from that individual will be saved.

Please refer to the TN01 Laboratory Manual for complete specimen destruction instructions as well as the Specimen Destruction Request form.

Note: If a participant determines that they do not want their samples stored, whether during enrollment or the course of the study, they are no longer eligible to participate in the Natural History/Pathway to Prevention Study. Please refer to section 5.12.2 to complete the “NH07 Change of Status” form.

6. INSTRUCTIONS FOR PARTICIPANT TRANSFER AND REMOTE STUDY VISITS

6.1 Participant Transfer

6.1.1 Originating Site Procedures

If a participant needs to transfer from one site to another during the course of the study then the transferring site (originating site) should do the following:

- Step 1. Contact the TNCC and notify them of the proposed participant transfer.
- Step 2. Determine the most suitable new site for the participant.
- Step 3. Provide the participant with contact information for the new site. Inform the participant that they will need to contact the new site's main contact within 7 days.
- Step 4. Contact the new site's main contact ASAP and inform them that a participant from your site will be transferring to them soon. You can provide information about where the participant is (time-point) in the study. You CANNOT provide any PHI to the new site until after the participant signs a HIPAA authorization and all other required forms at the new site.
- Step 5. Review all data and e-CRF's; complete and enter all missing data and attempt to reconcile any missing or outstanding tests results/source documents.
- Step 6. Once all data has been entered/reconciled and the participant has signed the new site's HIPAA authorizations, the originating site should navigate to the PRN form NH20 Permanent Participant Site Transfer and transfer the participant to the new site. See section 9.4 for instructions on how to access PRN forms.
- Step 7. Notify the new site that the participant has been transferred in the online system.

6.1.2 New Site Procedures

- Step 1. Once the originating site has made contact, wait for a call or email from the participant. If the participant has not made contact within 7 days, contact the originating site for direction.
- Step 2. Once the participant has made contact, schedule the participant for a visit or mail the new site consent forms and HIPAA authorizations to the participant for their review.
- Step 3. If the participant wishes to continue participation at the new site, bring the participant to the new site to sign the consent forms and HIPAA authorizations.
- Step 4. The new site should notify the originating site when the participant has signed the consent forms and HIPAA authorizations.
- Step 5. The originating site will notify the new site when participant has been transferred in the online system.

6.2 Remote Participant Visits

6.2.1 Collecting Specimens at an Unapproved Site

A participant may have samples collected at a physician's office or at another site that is not approved for this protocol. This would be a **specimen collection visit**. However, a **study visit** should not be completed.

The **unapproved site** refers to the site that is not approved under this protocol but will conduct a single visit for the participant.

The **enrolling site** is the site with full approval for the protocol and is the site in which the participant is currently enrolled.

Procedures:

- Step 1. The unapproved site needs to be currently approved by TrialNet for at least one TrialNet protocol. This approval must be on file at the TNCC OR be a lab vendor.
- Step 2. The unapproved site only conducts procedures that they already conduct under the approval of another TrialNet protocol or for which they have appropriate training/resources already in place.
- Step 3. The unapproved site **will not use** any of the online specimen collection forms for the visit.
 - a. The unapproved site should use its own source documents for the visit.
- Step 4. The unapproved site **will not use** the online Specimen Management System (SMS).
- Step 5. The site may choose to use its own supplies to collect specimens or may request a study kit per its Clinical Center's current procedure.

- Step 6. Upon completion of the study visit, the unapproved site will send *all* samples collected and source documents via FedEx to the enrolling site immediately.
- Step 7. The enrolling site will enter the visit online using online specimen collection forms, etc. and use the online specimen shipment system to ship specimens to the proper lab.

Please note: Reimbursement for the specimen collection will be sent to the enrolling site. It will be the responsibility of the enrolling site to distribute proper reimbursement to the unapproved site.

7. Informed Consent

Prior to site activation the TNCC will review all initial consents for all sites. The review will be performed to ensure all site's consents adhere to the guidelines below. If the TNCC requires any changes the site will be notified and should make the changes prior to submitting to their IRB.

After the initial review, sites should submit all amended consents (with tracked changes) to the TNCC prior to submitting the amended consent to their IRB. Once the IRB has approved the consent, a stamped copy should be submitted to the TNCC.

7.1 Required Elements of Informed Consent

The following include all required elements of informed consent per the Code of Federal Regulations (21 CFR 50.20 and 45 CFR 46.116) and the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) E6 guidance. Each element must be present in order for an informed consent form to be valid.

- 1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- 2) A description of any reasonably foreseeable risks or discomforts to the subject.
- 3) A description of any benefits to the subject or to others which may reasonably be expected from the research.
- 4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- 5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.
- 6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

- 7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- 8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Additional Elements of Informed Consent: When appropriate, one or more of the following elements of information shall also be provided to each subject:

- 1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
- 2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
- 3) Any additional costs to the subject that may result from participation in the research.
- 4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- 5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
- 6) The approximate number of subjects involved in the study.

Applies only to protocols approved after March 12, 2012:

When seeking informed consent for applicable clinical trials, as defined in 42 U.S.C. 282(j)(1)(A), the following statement shall be provided to each clinical trial subject in informed consent documents.

"A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

Each site's Institutional Review Board (IRB) or Ethics Committee is responsible for ensuring approved informed consent forms contain all required elements. The TrialNet Coordinating Center (TNCC) will perform a secondary review of all consent forms submitted by sites for required elements. If the TNCC discovers a missing element, the site will be required to submit an amendment to their IRB or Ethics Board prior to utilizing the consent form.

7.1.1 Assent of Children

Sites should follow their local institutional policy regarding obtaining assent from minors. Once the minor reaches the age of 18, the participant should be consented following the procedures documented in section 7.2- Informed Consent Process.

7.1.2 Consent for Stored Samples

Participants will be asked to provide consent for long-term storage of any remaining blood samples in the NIDDK Repository *after TrialNet is over*. (Note: those who decline to have their samples stored after TrialNet is over can still participate in the Natural History/Pathway to Prevention Study.)

However, in order to participate in the Natural History Study, participants are required to provide consent for stored samples *while TrialNet is ongoing*. Participants have the right to withdraw their consent to store samples while TrialNet is ongoing and to have their stored samples destroyed to the extent possible. However, the participant may no longer continue in the Natural History Study.

Purpose: At the Natural History/Pathway to Prevention Baseline and Semi-Annual Monitoring Visits, samples will be drawn for future studies to evaluate immune function and genetics. The samples will include serum, whole blood for RNA extraction, and whole blood for PBMC/plasma extraction. Samples may be used for the following purposes: plasma for the evaluation of islet autoantibody epitope, affinity, isotyping and proteomics based on assessment of immune responses, PBMC for the evaluation of immune cell function. Whole blood RNA will be tested for immune cell frequency and function by gene expression analysis.

For adults, the maximum amount of blood drawn for all tests combined will be 10.5 mL/kg or 550 mL (about 2 cups), whichever is greater, every 8 weeks. For those under age 18, we will take up to 5 mL (about 1 tsp) for every kg (2.2 lbs) of body weight per visit and up to 9.5 mL/kg over an 8-week period. For example, the maximum amount of blood drawn at one visit for a child weighing 55 lbs will be about ½ cup (125 mL; 25 tps). Blood volume limits may vary according to a site's institutional IRB – each site must ensure they are following their IRB's blood volume guidelines.

7.2 Informed Consent Process

7.2.1 Administration of the Informed Consent Process

Informed consent is more than just a signature on a form; it is a process of information exchange including, reading and signing the informed consent document, subject recruitment materials, verbal instructions, question/answer sessions and measures of subject understanding.

Informed consent should be obtained from each research subject before any study procedures are completed. Sites should verify that the participant has initialed and signed where needed. All staff members that are allowed to obtain consent should list that designation on the SDL.

In addition to signing the consent, the subject/representative should enter the date of signature on the consent document, to permit verification that consent was actually obtained before the subject began participation in the study. If consent is obtained the same day as a study procedure, the subject's medical records/case report form should document that consent was

obtained prior to that procedure. A copy of the consent document must be provided to the subject and the original signed consent document should be retained in the study records.

Source: <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126431.htm>

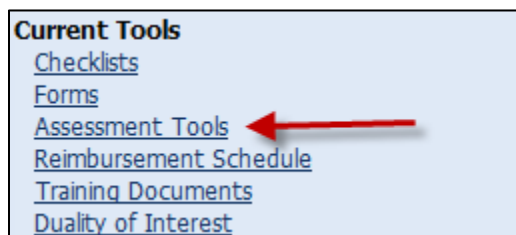
7.2.2 Documentation of the Informed Consent Process

The FDA defines informed consent as a process rather than a form. Therefore, documentation of the informed consent *process*, in addition to the signed form, is recommended. The TNCC recommends the following two options for documenting the informed consent process on site:

Standard Operating Procedure (SOP): Sites may create an SOP to be filed in the study regulatory file which outlines the sites' process of obtaining informed consent.

Informed Consent Process Checklist: Site may create a checklist outlining all informed consent procedures to be included in each individual subject chart.

The TNCC has created a template consent process statement and template checklists which conform to these guidelines. The templates are located on the members website in the TN01 protocol home page under Assessment Tools:



If the site chooses to create a site-specific consent process statement the following is a list of recommended elements to include in the informed consent process documentation:

- All of the subject's questions were answered/concerns addressed.
- Subject was given time to review the consent form and to discuss participation in this study with family members/others.
- The subject has agreed to participate in the study and signed/dated a valid consent form *prior to the start of any study procedures*.
- Discussed, explained and reviewed the consent form with the subject.
- Privacy was maintained throughout the informed consent process.
- A copy of the consent form was given to the subject.

For questions related to Informed Consent, please send queries to Regulatory@epi.usf.edu

7.2.3 Consent Revisions

Informed consent obtained at a clinical site should follow all standard procedures. The participant must sign a revised IRB approved Informed Consent Form/Assent with each revision of the document.

7.2.4 Annual Re-Consenting of Participants

Annual re-consenting of participants occurs to ensure that participants continue to be informed about the study as it progresses. Trial Coordinators should review the consent form with each participant annually to review the purpose of the study, the risks and benefits, and new information that has been learned since the previous consent. Trial Coordinators should reassess the participant's interest in continuing in the study and address all questions the participant may have. It is recommended that Trial Coordinators note the discussion in the study chart and include the date and discussion points in the notes.

If the IRB at the site requires a new consent form be signed annually, Trial Coordinators should administer the consent to the participant annually and keep the original in the participant's study chart.

8. Data Management

8.1 Introduction

All study data is collected via the secure web-based Protocol Management Tools system created in collaboration with the TrialNet Coordinating Center and will comply with all applicable guidelines regarding patient confidentiality and data integrity.

Registration of participants on this protocol employs an interactive data system in which the clinical site will attest to the participant's eligibility as per protocol criteria and that an appropriate informed consent has been obtained. IRB approval for the protocol must be on file at the TNCC before accrual can occur from the clinical site.

The TNCC uses a system of coded identifiers to protect participant confidentiality and safety. Each participant enrolled is assigned a local identifier by the enrollment site. Only the registering site will have access to the linkage between this number and the personal identifier of the participant. When the participant is registered in the study, using the TNCC provided web-based registration system, the system will assign a six-digit Participant ID number. Thus each participant will have two codes; the local one that can be used by the registering site to obtain personal identifiers and a second code assigned by the TNCC. In this fashion, it is possible to protect against data keying errors, digit transposition or other mistakes when identifying a participant for data entry since the TNCC requires that the numbers match to properly identify the participant.

8.2 Protocol Tool Management

The TNCC secure web-based Protocol Management Tools system includes the capability to capture and integrate many different types of data. Appropriate error checking occurs as data is entered employing range and relational checks for data consistency.

User Name and Password: A username and password will be issued to all personnel by the TNCC. The user will be required to change the standard password the first time he or she logs into the system. If you don't have or don't remember your username or password, you can get this information by contacting the study liaison or sending an email to TrialNet_CRAs@epi.usf.edu. Please do not share your username and password. Any data entered or changed in the system will be audited by username.

8.3 System Requirements

In order to use the web-based Protocol Management Tools system you need to have:

Hardware and software:

- Access to a PC running Windows 98, 2000, XP, or ME.
- Internet Explorer 6.0 or higher.
- Internet connectivity. High-speed broadband or better connection is recommended.
- Adobe Reader is required to download some of the documents for this study. To download the Adobe Reader go to www.adobe.com and click on the Get Adobe Reader button.
- Software to zip/unzip files.

General considerations when using a web-based system:

- You can access this system from any machine that has the hardware and software described above, no special installation is required.
- No intensive training needed to use this application. If you are familiar with the use of a browser you already have the basic knowledge.
- Updates to the system will be done on the server without user disruption.
- The system is dependent on the Internet / Intranet for application availability. If you lose or don't have internet connectivity you won't be able to use the system.
- Web interfaces are not as mature as they are for more traditional client/server model. This means that some nice features you are used to might not be available to you.
- Most of the time you are disconnected from the server while using a web application. This means that if you close your form without clicking the Submit button you will lose all the information you just entered since the system won't ask (as your word processor does) if you want to save your data before closing. Also, if you don't click the Submit button for a period of time your session expires and you will be asked to login again. In this case, when you login again you will be able to save your work.
- It is strongly recommended that you use the navigation menus and button provided by the system instead of the Back and Forward buttons in your browser.

8.4 International Considerations

Overview: All study data is collected via the secure web-based Protocol Management Tools system created in collaboration with the TrialNet Coordinating Center and will comply with all applicable guidelines (e.g. USA FDA 21CFR11, USA HIPAA Privacy Act 45CFR 160 and 164, WMA's Declaration on Ethical Considerations Regarding Health Databases (2002), CIHR Best Practices for Protecting Privacy in Health Research (2005), Data Protection Directive 95/46/EC of the European Parliament and of the Council (1995), et al) regarding patient confidentiality and data integrity.

Data Security: The TNCC has created an encrypted central website for TrialNet using 128-bit secure socket layer technology that is password protected. Each protocol area is secured by allowing only individuals who have current ethic's board approval for a protocol to access the protocol area. Furthermore, additional security roles vet each user by site only allowing access to subject data entered by each user's site; in this way only the consenting site may view data for their subjects

User Name and Password: A username and password will be issued to all personnel by the TNCC. All individuals issued a password must be identified as a qualified person (appropriate

human subjects training, ethic's board approval for specific role, etc) by each site's Principal Investigator on a continuously maintained site delegation log (site delegation of authority log). The user will be required to change the standard password the first time he or she logs into the system. All users are instructed to keep their login and password secure and are not allowed to share their username and password.

Training of Users: In addition to human subjects training, all users are required to be trained on each specific protocol for which they are entering data as well as use of the online systems and tools. The TNCC has created a media center in which taped presentations are stored (by topic/by protocol) which allows sites/TrialNet personnel to view training presentations on relevant systems/protocol/study topics. The TNCC tracks the viewing of trainings to ensure individuals accessing the online system are appropriately trained.

Qualified Persons: All individuals at the TNCC responsible for systems are appropriately trained (computer science/networking background, secondary education or greater) to create and maintain web systems and databases. Additionally, all individuals at the TNCC are required to complete yearly human subjects training and are approved for his/her specific role by the USF Institutional Review Board (IRB).

Data Errors: Any data entered or changed in the system will be audited by username. Audit database tables are generated each time the system is accessed, subject data is viewed, added, updated, or deleted. Appropriate error checking occurs as data is entered employing range and relational checks for data consistency.

Registration of participants on this protocol employs an interactive data system in which the clinical site will attest to the participant's eligibility as per protocol criteria and that an appropriate informed consent has been obtained. Ethic's board/IRB approval for the protocol must be on file at the TNCC before accrual can occur from the clinical site.

The TNCC uses a system of coded identifiers to protect participant confidentiality and safety. Each participant enrolled is assigned a local identifier by the enrollment site. Only the registering site will have access to the linkage between this number and the personal identifier of the participant (personal identifiers stored at the site). When the participant is registered in the study, using the TNCC provided web-based registration system, the system will assign a Participant ID number. Thus each participant will have two codes; the local one that can be used by the registering site to obtain personal identifiers, and a second code assigned by the TNCC. In this fashion, it is possible to protect against data keying errors, digit transposition or other mistakes when identifying a participant for data entry since the TNCC would require that the numbers match to properly identify the participant.

9. Online Data Capture System

9.1 Overview and Basic Functionality

9.1.1 Login/Navigate to the TN01 Protocol Manager Area

Step 1. Procedure to login and navigate to the TN01 protocol manager area: Log into TrialNet Members Site: <http://www.diabetestrialnet.org/members.htm>.



Step 2. Under Members Login Screen enter User Name and Password.

Type 1 Diabetes TrialNet

Members Login

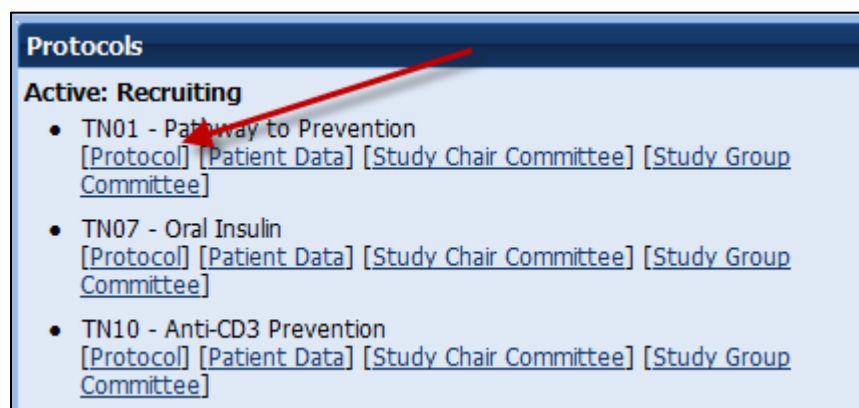
User Name:

Password:

Login

[Forgot your password?](#)

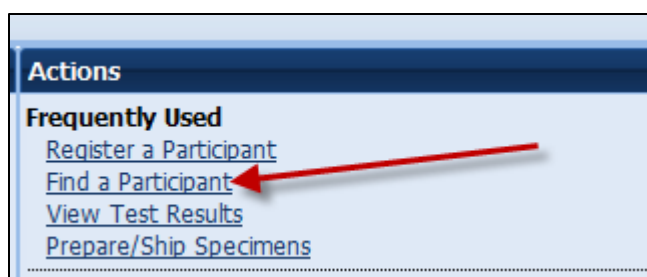
Step 3. Navigate to the "Protocols" portlet. Under 01, select "Protocol."



9.1.2 Finding a Participant

Note: This procedure will be done for every visit.

Step 1. Procedure to find participant: Once in TN01 Protocol, navigate to the "Actions" portlet and select "Find Participant."

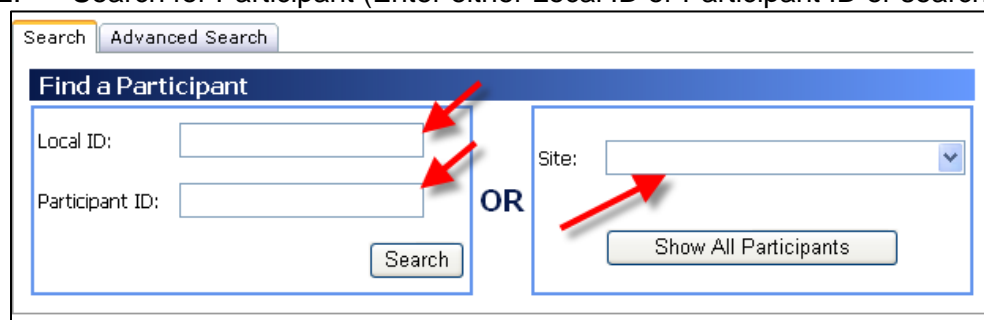


Actions

Frequently Used

- [Register a Participant](#)
- [Find a Participant](#)
- [View Test Results](#)
- [Prepare/Ship Specimens](#)

Step 2. Search for Participant (Enter either Local ID or Participant ID or search by site).



Search Advanced Search

Find a Participant

Local ID:

Participant ID:

OR

Site:

Search

Show All Participants

Step 3. The list of subjects matching entered criteria will populate below the search box. Click on Local ID (in blue text color). This will open the Participant Detail Screen

Local ID	Participant ID	Letters	Study Site	Registration Date	Participant Status
1202020202	100309	DEM	12 - University of Texas [12]	20 Mar 2009	Registered
120900086	100301	ABC	12 - University of Texas [12]	09 Mar 2009	Eligible
081201	100295	tnm	12 - University of Texas [12]	05 Mar 2009	Eligible
2009022401	100288	WOT	12 - University of Texas [12]	24 Feb 2009	Eligible

Page 1 of 1

Total Records: 4

[\[First Page\]](#) [\[Previous Page\]](#) [\[Next Page\]](#) [\[Last Page\]](#)

9.1.3 Registering a Participant

Step 1. Log into TrialNet Members Website and navigate to the Protocols portlet. Select the "Protocol" link under TN01 Pathway to Prevention.

Protocols

Active: Recruiting

- [TN01 - Pathway to Prevention](#)
[Protocol] [Patient Data] [Study Chair Committee] [Study Group Committee]
- [TN07 - Oral Insulin](#)
[Protocol] [Patient Data] [Study Chair Committee] [Study Group Committee]
- [TN10 - Anti-CD3 Prevention](#)
[Protocol] [Patient Data] [Study Chair Committee] [Study Group Committee]

Step 2. Once in TN01 Home Page, navigate to the Actions portlet and select “Register Participant.”

Actions

Frequently Used

- [Register a Participant](#)
- [Find a Participant](#)
- [View Test Results](#)
- [Prepare/Ship Specimens](#)

Step 3. Once the Register Participant Screen is displayed complete the following fields

- Local ID: The site can enter the desired local ID for the participant. This can include numbers and letters.
- Letters: Enter three letters.
- Participant ID: ID should remain the same for interventional studies

Note: PID should be skipped if first time participant on TrialNet study.

d. Site: Select applicable site.

Step 4. Click on the Register Participant. A success message with the auto-generated Participant ID will appear. For example :

Register a Participant

Local ID: * **Site creates Local ID** →

Letters: **Any three letter code assigned by the site to identify an individual** →

Participant ID: (Enter only if you wish to register a participant that has already been registered on a different protocol.)

Site: **Click arrow to select your site** →

Select after entering Local ID, Letters and Site → **Register Participant**

You have successfully registered Participant ID : 100308

Step 5. Record the Participant ID for your source documents.

Step 6. If you want to view the participant details for the newly registered subject, select the “Participant Details” button at the bottom of the “Register a Participant” box.

The screenshot shows a web form with a dropdown menu and two buttons: 'Participant Details' and 'Register Participant'. A red arrow points to the 'Participant Details' button.

9.1.4 Save and Close e-CRFs

Note: This procedure will be the same after each e-CRF is completed.

Step 1. Procedure to save and close-out form: After entering the data select “Save”.

The screenshot shows three buttons: 'Save', 'Print', and 'Close Window'. A red arrow points to the 'Save' button.

The message “Forms saved successfully” will display.

The screenshot shows a Microsoft Internet Explorer dialog box with a yellow warning icon and the text 'Form saved successfully.' and an 'OK' button.

Step 2. Select Close Window, the message, “You must click “Save” to save the data on this form before you close. “Are you sure you want to close this form?” will display, Select “OK.”

The screenshot shows a Microsoft Internet Explorer dialog box with a question mark icon and the text 'You must click 'Save' to save the data on this form before you close. Are you sure you want to close this form?' and 'OK' and 'Cancel' buttons.

Step 3. The following message will display, “The page cannot be refreshed without resending the information Click Retry to send the information again, or click Cancel to return to the page that you were trying to view.” Select Retry and screen will automatically return to Participant Details

The screenshot shows a Microsoft Internet Explorer dialog box with a yellow warning icon and the text 'The page cannot be refreshed without resending the information. Click Retry to send the information again, or click Cancel to return to the page that you were trying to view.' and 'Retry' and 'Cancel' buttons.

9.1.5 Save and Close Specimen Collection Forms

Note: This procedure will be the same for each collection form

Step 1. Save the information entered in the collection form by clicking on "Save All."

Step 2. Close the form by clicking on "Close." You will be prompted to save changes if you have made changes that have not yet been saved.

Test Name	Barcode	Reserved	Date of Draw	Not Collected	Not Required	Priority	
Serum - autoantibodies	TNSSS1	<input type="checkbox"/>	20 Nov 2009	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	X
Serum - chemistries	TNSSS2	<input type="checkbox"/>	20 Nov 2009	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	X

Please review the TrialNet Specimen Management System User Manual for potential error messages you may receive when attempting to save a collection form and additional information regarding collection forms.

9.1.6 Form Required Fields

There are two kinds of required fields on every form:

Fields required to save a form; These fields have a red asterisk next to them. Examples of these are Date of Visit and Interviewer User ID (required on every form in order to save a form).

Date of Visit: * 6 Mar 2009 [Date](#)

Interviewer User ID: * 54491

Fields required in order for the form to be complete: These fields have a blue asterisk next to them.

A description of this requirement is at the top of every form:

* These fields are required in order to SAVE the form

* These fields are required in order to COMPLETE the form

9.1.7 Clear ALL Data from a Form

If you find you have mistakenly entered wrong data on a form, you can clear all data on the form as long as you are the person who entered the data on the form (determined based on the Interviewer user ID entered in the form).

Step 1. Navigate to the form which you would like to clear.

Step 2. Click on the button entitled “Clear Form” in the upper right hand corner of the screen.

Protocol # TN01 - Natural History...

Participant ID: 203336	Date of Registration: 19 Sep 2011
Local ID: nk101	Letters: NCK
Status: Eligible	Date of Baseline Exam: 19 Sep 2011
Site: Benaroya Research Institute [10]	

NH01 - Screening Information

* These fields are required in order to SAVE the form

* These fields are required in order to COMPLETE the form

Date of Visit: * 19 Sep 2011 [Date](#)

Interviewer User ID: * 54722

Eligibility Information

A. Participant Eligibility

1.) Date screened:* 19 Sep 2011

2.) Age* 10 years

3.) Do you have a relative with T1D?* ☒ Yes ☐ No

4.) If yes, what degree of relative? ☒ 1st ☐ 2nd or 3rd

5.) Do you have diabetes?* ☐ Yes ☒ No

Please indicate participant location:* ☐ North American ☒ International

B. Participant Information

1.) Name

Last

First

Middle Initial

2.) Address

Street Address

Step 3. The page will navigate to a description of the form you are about the clear (Clear Form Data box). If you are certain you wish to clear out all data on the form, click the button “Clear.”

Step 4. A pop-up window will display asking you if you are certain you want to clear the form. If you are certain, click “Ok.”

Step 5. You will know the form cleared successfully as green text will appear under the Clear Form Data box.

Step 6. Click the “Close” button and you will navigate back to the participant’s details. If unable to clear the form, please contact the TNCC for further directions.

9.1.8 Clear ALL Data from a Collection Form

For instructions on how to clear data from a Collection Form please refer to the Specimen Management System User Manual

9.2 Participant Details

Timepoint	Event Title	Tracking
Screening	Registration Form	
	Pathway to Prevention Visit Assignment Form	Tracking
	NH01 - Screening Form	
	NH01F - Family History Form	
	Screening Specimen Collection	
	Screening Visit Start Date	Tracking

- Time Point – When this event occurs in the timeline that starts at registration (e.g. Screening, Baseline, Visit 1, etc)
- Event Title – Title of the Event/Form (e.g. Demographics, Family History, Physical Exam, etc)
- Tracking – The Event Tracking Form. This form should be completed if a visit was missed

Event Tracking Form

Event name: **Screening Visit Start Date**
Time point: **Screening**

* These fields are required in order to SAVE the form

Event Done? *
☒ Not done
☐ Done

Why wasn't this done?

☐ Participant missed appointment
☐ Participant/parent refused
☐ Unable to obtain sample
☐ Unable to contact subject
☐ Illness
☐ Other

- Due Date – When the event should occur according to the Schedule of Events from the protocol.
- Last Modified Date – The last date the information regarding this event was modified.
Note: Looking at the form without saving will not change this date.
- Event Status –
 - If the status is blank, then no data has been entered in the event/form.
 - If the status is Incomplete there are required data elements missing.
 - If the status is Complete all required data elements have been entered and the form has been saved (fields on the form with blue asterisks).

- If the status is Unverified then the data has been mapped from previous data and the site has not yet reviewed and saved the form to ensure the data captured in the form is accurate.
- If the status is Complete all required data elements have been entered and the form has been saved (fields on the form with blue asterisks).
- If the status is Not Done then the visit was missed.

Please note, for all online data capture forms, if a question is not applicable, please leave the response choices blank (i.e. if the participant is a male and there are items that pertain to females only please do not select a response choice of “yes” or “no” and instead leave the response blank).

9.3 Visit Forms

9.3.1 Data Entry for All Visit Forms

Step 1. Be sure the Source Document is completed prior to completing forms

Step 2. Under Event Title select the form you want to open.

Timepoint	Event Title	Tracking	Due Date	Last Modified Date	Event Status
Screening	Screening Informed Consent Verification	Tracking	19 Mar 2009		

Step 3. Once the form displays, enter Date of Visit and your Interview User ID.

Step 4. Complete all sections of the form

The screenshot shows the 'Pathway to Prevention Visit Assignment Form'. At the top, there are two red asterisks indicating required fields for saving the form, and two blue asterisks indicating required fields for completing the form. The 'Date of Visit' field is annotated with a red arrow pointing to the date picker (6 Jul 2012) and a yellow box labeled 'Enter Date of Visit'. The 'Interviewer User ID' field is annotated with a red arrow pointing to the text input (99999) and a yellow box labeled 'Enter Interviewer User ID'. Below these, the question 'On which study phase is this participant currently enrolled? *' is shown with radio button options: Screening, Baseline Monitoring, DPT-1 Monitoring Entry, and Control Monitoring Entry. A red arrow points to the 'Screening' option, and a yellow box labeled 'Select Screening Phase' is next to it. At the bottom, there are 'Save', 'Print', and 'Close Window' buttons.

Step 5. After entering data, please reference section 9.1.4 Save and Close e-CRF form.

Step 6. Complete data entry for all forms for each study visit. (Note: data should be entered for all forms within 30 days of the visit)

9.3.2NH01 – Screening Form

Step 1. Be sure the Source Document is completed prior to completing forms

Step 2. Under Event Title, click on NH01 – Screening Form.

NH01 - Screening Form	Tracking
---------------------------------------	--------------------------

Step 3. Once the form displays, enter date of Visit and your Interviewer User

NH01 - Screening Information			
* These fields are required in order to SAVE the form			
* These fields are required in order to COMPLETE the form			
Date of Visit:	*	26	Sep 2011 Date
Interviewer User ID:	*	54722	

Step 4. Complete the form based on your source documents and enter the following information listed:

- a. Eligibility Information
 - i. Date Screened
 - ii. Age
 - iii. Relative with T1D
 - iv. Degree of relative with T1D
 - v. Indicate if the participant has T1D or not
 - vi. Indicate location.
- b. Participant Information (for North American Sites only)
 - i. Name
 - ii. Address
 - iii. Phone Number
 - iv. Email address (optional)
 - v. Social security number (optional)
 - vi. Date of Birth
 - vii. Sex
 - viii. Ethnicity
 - ix. Race
 - x. Name of guardian (if applicable)
 - xi. Relationship to participant (if applicable)
 - xii. Indicate how the participant heard about TrialNet.
- c. Clinical Site
 - i. Consent to store samples after TrialNet is over
 - i. Date signed consent form
 - ii. Consent to Negative Cohort.

9.3.3NH01F – Family History Form

Step 1. Be sure the Source Document is completed prior to completing forms.

Step 2. Under Event Title, click on NH01F – Family History Form.

NH01F - Family History Form	Tracking
---	--------------------------

Step 3. When the form displays, enter Date of Visit and your Interview User ID.

Step 4. Complete Family History section.

Step 5. After entering data, please reference section 9.1.4 Save and Close e-CRF Forms.

9.3.4Specimen Collection Form: Main Collections

Each visit will have one Specimen Collection Form. The form will take into account age/weight restrictions and will be limited to only those samples required for that particular participant during that specific visit. Main collections include all specimens except for tolerance collections. Tolerance collections include OGTTs, IVGTTs, and MMTTs.

Please refer to the TrialNet Specimen Management System User Manual for additional information regarding completion of Specimen Collection forms.

9.3.5Specimen Collection Form: Tolerance Collections

Tolerance collections include OGTTs, IVGTT, and MMTTs. If a tolerance collection is required for a visit, a "Tolerance Collection" tab will appear in the specimen collection form for that visit.

Main Collection	Tolerance Collection
Save All Show Instructions Print Collect QC Prepare Specimen Shipment Browse Specimens Clear Group Close	

After completing the Main Collections navigate to the “Tolerance Collection” by selecting the “Tolerance Collection” tab.

Please refer to the TrialNet Specimen Management System User Manual for additional information regarding completion of Specimen Collection forms.

9.3.6NH04 – Baseline Monitoring

Step 1. Be sure the Source Document is completed prior to completing forms.

Step 2. Under Event Title, select NH04 – Baseline Monitoring Risk Assessment.

NH04-Baseline Monitoring Risk Assessment	Tracking
--	--------------------------

Step 3. When the form displays, enter Date of Visit and your Interviewer User ID.

NH04-Baseline Monitoring Risk Assessment	
* These fields are required in order to SAVE the form	
* These fields are required in order to COMPLETE the form	
Date of Visit:* 6 Jul 2012 Date	Enter Date of Visit
Interviewer User ID:* 99999	Enter Interviewer User ID

Step 4. Complete the following sections for this form:

- a. Eligibility
- b. Informed Consent and Permissions
- c. Medical history
- d. Height, Weight and Vital Signs
- e. Prior Research Participation.

NH04-Baseline Monitoring Risk Assessment		
* These fields are required in order to SAVE the form		
* These fields are required in order to COMPLETE the form		
Date of Visit:	<input type="text"/>	<input type="text"/> Date
Interviewer User ID:	<input type="text"/>	
B. ELIGIBILITY		
1. Has the participant been diagnosed with type 1 diabetes (T1D)?	<input type="radio"/> Yes <input type="radio"/> No	
2. Has the participant ever previously used or is currently using medications for the control of hyperglycemia (e.g. Insulin, Oral Hypoglycemic agents including Sulfonylureas, Metformin, Thiazolidinediones, Alpha-Glucosidase Inhibitors, Meglitinides, GLP-1 Mimetics and DPP-4 Inhibitors)?	<input type="radio"/> Yes <input type="radio"/> No	
3. Does the participant have known severe inactive diseases, and/or diseases which are likely to limit life expectancy or lead to use of immunosuppressive or immunomodulatory therapies during the course of the study?	<input type="radio"/> Yes <input type="radio"/> No	
4. For females of child bearing age/potential, is the participant currently pregnant?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> N/A	
If the participant answered YES to any of questions 1-4, he/she is <u>ineligible</u> to participate in the study.		
If ineligible:		
<ul style="list-style-type: none"> DO NOT fill out the remainder of this form. Discard this form Complete a Change of Status Form (NH07) Complete a Diabetes Onset Form (NH08) if the answer to question 1 is YES 		
C. INFORMED CONSENT AND PERMISSIONS		
1. Did participant consent to continued storage of residual blood samples in the NIDDK Repository after TrialNet has ended? *	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> N/A	
2. Date participant signed the Monitoring Informed Consent Form:	<input type="text"/>	
D. MEDICAL HISTORY		
Has the participant been told by a physician that he/she has any of the following conditions?		
Condition/Disease	a. Ever been told?	b. Within the last year?
1. Asthma	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Yes <input type="radio"/> No
2. Celiac Disease	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Yes <input type="radio"/> No
3. Inflammatory Valve Disease	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Yes <input type="radio"/> No
4. Addison's Disease	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Yes <input type="radio"/> No
5. Vitiligo	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Yes <input type="radio"/> No
6. Thyroid disease	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Yes <input type="radio"/> No
7. Psoriasis	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Yes <input type="radio"/> No
8. Alopecia (Hair Loss)	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Yes <input type="radio"/> No
9. Rheumatologic disease - Within the last year (e.g. Lupus, Rheumatoid Arthritis, etc.)	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Yes <input type="radio"/> No
10. Multiple Sclerosis	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Yes <input type="radio"/> No
11. Other autoimmune diseases	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Yes <input type="radio"/> No
a. If YES, specify: <input type="text"/>		

E. HEIGHT, WEIGHT AND VITAL SIGNS			
<i>Collect the following physical assessments:</i>			
<i>Note: The participant should rest for 5 minutes before these assessments are performed</i>			
1. Seated arm blood pressure:	<input type="text"/> mmHg	<input type="text"/> mmHg	
	Systolic	Diastolic	
2. Weight:	<input type="text"/> kg	<input type="text"/> lbs	
3. Height (If participant <18 years use a stadiometer if available):	<input type="text"/> cm	<input type="text"/> in	
<i>Please make sure height and weight are in the correct units.</i>			
F. PRIOR RESEARCH PARTICIPATION			
1. Has the participant ever participated in a prevention study for type 1 diabetes?		<input type="radio"/> Yes <input type="radio"/> No	
a. If Yes, name of study/studies (if known): <input type="text"/>			
2. Did the participant participate in DPT-1		<input type="radio"/> Yes <input type="radio"/> No	
a. If Yes, record the DPT-1 participant ID number (if known): <input type="text"/>			
<input type="button" value="Save"/> <input type="button" value="Print"/> <input type="button" value="Close Window"/>			

9.3.7NH05 – Follow-Up Risk Assessment

Step 1. Be sure the source document is completed prior to completing forms.

Step 2. Under Event Title, select NH05 – Follow-Up Risk Assessment.

	NH05 - Follow-Up Risk Assessment Phase 3	
--	--	--

Step 3. When the form displays, enter Date of Visit and you Interviewer User ID.

NH05 - Follow-up Risk Assessment Form			
<i>* These fields are required in order to SAVE the form</i>			
<i>* These fields are required in order to COMPLETE the form</i>			
Date of Visit:*	6	Jul	2012
	Date	Enter Date of Visit	
Interviewer User ID:*	99999	Enter Interviewer User ID	

Step 4. Complete the following sections for this form:

- Eligibility
- Informed Consent and Permissions
- Medical History

Definition: PRN – “When necessary”

The forms available under the **Additional Study Forms/Events** are to be used when an event occurs outside of the specified visit window for a particular visit.

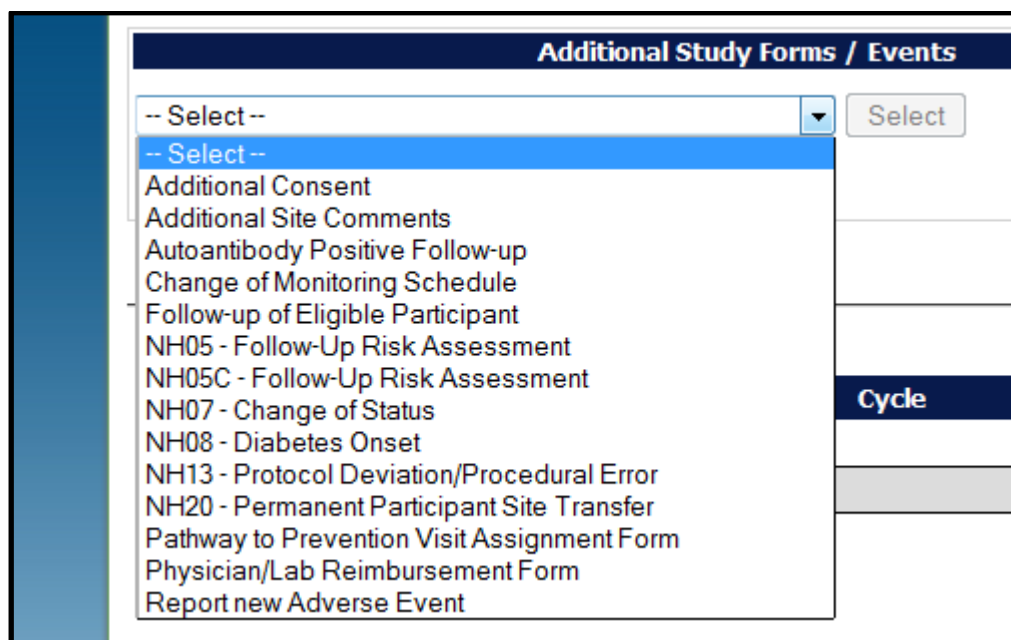
Forms available are as follows:

1. NH05 Follow-Up Risk Assessment – to be used when a visit occurs outside of a scheduled visit or window.
2. NH07 Change of Status – to be used when the status of a participant changes (subject withdrawals from study or is lost to follow up, etc.). Once participants are enrolled in the Natural History Study, they are enrolled for the duration of the Study (or until study endpoint is met). A change of status could involve the participant becoming inactive by not being able or willing to attend future follow-up visits. This form will also be completed if an inactive participant decides to return to active study participation by attending future follow-up visits. This form will collect information on the date of the change in status, as well as the reason for the change in status. Note that this form is completed each time a participant changes study status.
3. NH08 Diabetes Onset – to be used whenever it is determined a participant has developed Diabetes. The collected information includes hospitalization information, signs and symptoms of diabetes, and glucose levels.
4. NH13 Protocol Deviation – to be used whenever a protocol deviation occurs (samples are missed, etc.). A separate form must be completed for every unique protocol deviation that occurs, even if the subject is the same. The form obtains specific information on the deviation that has occurred, including the date the deviation occurred, the specific deviation that has occurred, as well as the reason for the protocol deviation.
5. NH20 Permanent Participant Site Transfer – to be used if a subject moves from one study site to another. The form collects information on the date the transfer is occurring and the number of the site to which the participant is transferring.
6. Report New Adverse Event – to be used when a subject experiences a reportable adverse event.
7. PRN Specimen Collection – to be used whenever a specimen is collected outside of a scheduled visit or window. Refer to the Specimen Management System (SMS) User Manual and TN01 Laboratory Manual for instructions on the selection and completion of PRN collection forms.

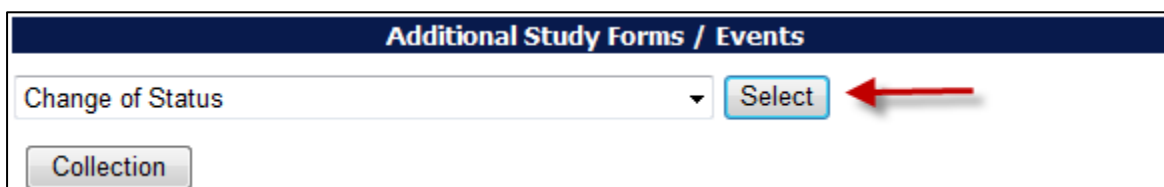
9.4.2 Open a New Additional Study Form/Event (PRN Form)

Step 1. From the participant details page, on the left side of the main screen, above the study schedule, the PRN forms are located in the drop-down box entitled “Additional Study Forms/Events.”

Step 2. Select the form needed from the list.



Step 3. Once you have selected the desired form, click the “Select” button.

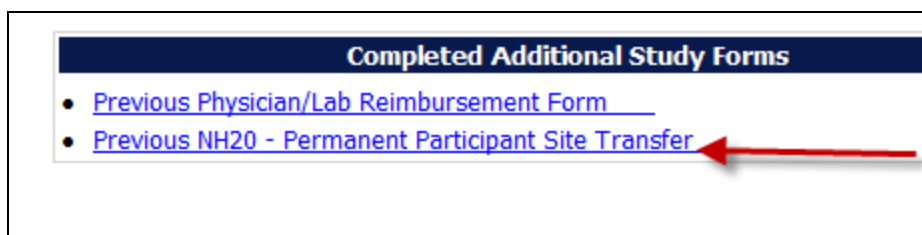


Step 4. A new window will open with the selected form.

9.4.3 Open a Previously Completed Additional Study Form/Event (PRN Form)

Step 5. From the participant details page, on the right side of the main screen, directly beneath the subject header, above the study schedule, is a list of all types of PRN forms previously completed for the participant.

Step 6. Select the type of previously completed PRN form you would like to view



Completed Additional Study Forms

- [Previous Physician/Lab Reimbursement Form](#)
- [Previous NH20 - Permanent Participant Site Transfer](#)

Step 7. A new window will open displaying a list of all PRN forms previously completed for the participant of the selected type. Select the specific form you wish to view.

Event date	Event Title
08 Apr 2009	NH07 - Change of Status
01 Oct 2008	NH07 - Change of Status

Step 8. The previously completed form will open in a new window.

9.4.4PRN Specimen Collection Forms

Please refer to the TrialNet Specimen Management System User Manual for additional information regarding the completion of PRN collection forms, Section 3.3.

10. ADVERSE EVENT REPORTING PROCEDURES

All adverse events will be reported to the TrialNet Data Safety and Monitoring Board (DSMB) by using the Adverse Events Data Management System (AEDAMS) described below.

10.1 Definitions and Data Descriptions

In this clinical research study, an adverse event (AE) is any occurrence or worsening of an undesirable or unintended sign, symptom or disease that is associated with study procedures. As an observational study, AE's occurring between study visits will not be reported unless deemed associated with study procedures. Development of diabetes including diabetes requiring hospitalization will be reported as study endpoint and will not constitute an AE or SAE unless it leads to death.

A serious adverse event, as defined by the U.S. Food and Drug Administration (FDA), includes those events that "result in death; are life-threatening; require inpatient hospitalization or prolongation of existing hospitalization; create persistent or significant disability/incapacity, or a congenital anomaly/birth defects."

To better define serious adverse events and to ease reporting, a standardized classification for adverse events, including a grading scale for severity, will be used. The classification TrialNet utilizes to report adverse events will be the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, with the exception of hypoglycemia and hyperglycemia, developed and

maintained by CTEP at National Cancer Institute. This classification provides a grade (1-5) to describe event severity; the severity grade determines whether an event is considered “serious” for purposes of TrialNet DSMB review.

Throughout the study, the investigator must record all adverse events on source documentation. Those that are Grade 2 or greater **and related to study procedures** must be reported on the appropriate adverse event form as described below. The investigator should treat participants with adverse events appropriately and observe them at suitable intervals until the events resolve or stabilize.

For this trial, an adverse event associated with the treatment or study procedures that suggests 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 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.
- is, in the opinion of the investigator, serious

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/or may require medical or surgical intervention to prevent one of the outcomes listed above.

An adverse event is considered **unexpected** when the nature (specificity) or severity of the event is not consistent with the risks described in the protocol, investigator brochure, or informed consent document for a particular protocol required intervention. Included in the unexpected definition are those events which are greater in severity or frequency than expected.

Data Descriptions:

A set of standard elements for adverse event data is collected across all studies in TrialNet. These elements include: Participant ID, reporter name & location, dates for event/event reported/date resolved, the event itself, event severity, whether it was expected and/or serious (as defined above), patient status, place of AE treatment (to further determine serious events), causality, and subsequent changes to protocol or consent form. Additionally, there is designated space for the reporter to write a description of the event and any other pertinent information. This standard set of data elements has been approved by all TrialNet investigators, the TrialNet Executive Committee, and the TrialNet Data and Technology Coordinating Center (TNCC).

Common Terminology Criteria for Adverse Events (CTCAE):

The values to describe adverse events will come from the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, with the exception of hypoglycemia and hyperglycemia, developed and maintained by CTEP at National Cancer Institute. The CTCAE v.3.0 was chosen because of its widespread use as a standard for adverse event reporting in clinical trials, its specific criteria for grading severity, and its ongoing maintenance from the National Cancer

Institute (NCI). Additionally, the NCI has provided mappings from CTCAE to MedDRA, the current standard for FDA reporting.

The CTCAE is organized broadly by categories. Each category is a broad classification of AEs based on anatomy and/or pathophysiology. Within each category, AEs are listed (alphabetically) accompanied by their descriptions of severity (grade). An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE must be associated with a grade. Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity of each AE based on this general guideline:

- Grade 1 = Mild AE
- Grade 2 = Moderate AE
- Grade 3 = Severe AE
- Grade 4 = Life-threatening or disabling AE
- Grade 5 = Death related to AE

Not all grades are appropriate for all AEs. Therefore, some AE's are listed with fewer than 5 options for Grade selection. (e.g., The adverse event "Nail Changes", listed in the Dermatology/Skin Category, only has options for Grades 1-3.) Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Using the CTCAE:

TrilaNet provides several resources for the proper use of CTCAE codes for adverse event reporting. Because the NCI has developed and maintained the CTCAE classification, the recommended educational materials are from the NCI. Each person entering data in the AE system should be given a copy of a small spiral-bound booklet titled "Common Terminology Criteria for Adverse Events (CTCAE), version 3.0." [NIH Publication No. 03-5410.] This booklet contains the entire CTCAE, with descriptions of each event and grade.

Additionally, the CTCAE can be accessed online from the NCI at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf

When coding an event, the reporter should consider the underlying pathophysiology or body system of the event, and go to that Category to look for the event. For example, nausea is found in the Gastrointestinal Category, arthritis is found under the Musculoskeletal/Soft Tissue Category. Embedded within the AE listings for all categories are "remarks", "Navigation Notes" and "Also Consider" additions, which should not be ignored.

- A 'Remark' is a clarification of an AE.
- An 'Also Consider' indicates additional AEs that are to be graded if they are clinically significant.
- A 'Navigation Note' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same Category unless the 'Navigation Note' states differently.

Sometimes the AEs listed for a category are "clustered" together using a supra-ordinate term. A supra-ordinate term is located within a Category and is a grouping term based on disease

process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word “select”. A supra-ordinate term helps organize a group of AEs within a category; an AE (from a select list of AEs listed below the specify comment) must be selected beyond the supra-ordinate term.

The Death Category is new. Only one Supra-ordinate term (‘Death not associated with CTCAE term’) is listed in this category with 4 AE options:

Death NOS;
Disease progression NOS;
Multi-organ failure;
Sudden death.

Note: Grade 5 is the only appropriate Grade for the Death Category. This AE is to be used in the situation where a death: 1.) cannot be reported using a CTCAE v3.0 term associated with Grade 5, or 2.) cannot be reported within a CTCAE category as ‘Other (Specify)’.

There is an AE option called NOS (Not otherwise specified) for each category that will require a description.

The NCI also posts an Index to the CTCAE at:

http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_index.pdf

This index is an alphabetical listing of clinical phenomena that can guide the reporter to the appropriate CTCAE category within to search for the event. For example, one can use the index to look up the concept “depression” and will subsequently be directed to the “Neurology” category and that “mood alteration” is the preferred term for this AE in the CTCAE. The index is a good resource to use for using synonyms and related terms to find the appropriate reporting category and term.

If the appropriate category of AE term cannot be found using the Index, please contact your TNCC liaison for guidance on finding the appropriate CTCAE term.

10.2 Reporting Timeline

Follow the timelines below for the reporting of adverse events:

- Within **24 hours** (of learning of the event), investigators must report any 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 SAEs within **5 working days** (of learning of the event).
- All other (suspected) AEs must be reported to the TNCC within **20 working days** of the notification of the event or of the site becoming aware of the event.

10.3 Directions for Reporting AE’s / System Description

10.3.1 Navigating to the Adverse Event Form

- Step 1. On the Participant’s Details page select “Report new Adverse Event” from the Additional Study Forms/Events dropdown list. Then press the Select button.

Additional Study Forms / Events

-- Select --

-- Select --

Additional Consent

Additional Site Comments

Autoantibody Positive Follow-up

Change of Monitoring Schedule

Follow-up of Eligible Participant

NH05 - Follow-Up Risk Assessment

NH05C - Follow-Up Risk Assessment

NH07 - Change of Status

NH08 - Diabetes Onset

NH13 - Protocol Deviation/Procedural Error

NH20 - Permanent Participant Site Transfer

Pathway to Prevention Visit Assignment Form

Physician/Lab Reimbursement Form

Report new Adverse Event

Select

Cycle

10.3.2 Reporting an Adverse Event

- Step 1. You will be directed to an “Adverse Event Reporting Form”. Complete this form to report an adverse event. The asterisked fields are required.
- To save this report, WITHOUT SUBMITTING, select “Save draft.”
 - NOTE: This option does not submit the AE. To submit an Adverse Event you must select the “submit for review” option. “Save draft” allows you to re-open the form later and submit the event at a later time.
 - To submit the report, click on “Submit for review.”
 - NOTE: Selecting “submit for review” automatically saves the event as well.
 - If the save is successful, you will see a success message. You may then close this window. If you do not see a success message, your report was not transmitted. Please resave, or contact your TNCC CRA immediately for assistance.

Adverse Event Reporting Form	
Initial Report	
* These fields are required in order to SAVE the form	
A. INTERVIEW INFORMATION	
Adverse event report date	<input type="text"/> (DD MMM YYYY) *
B. ADVERSE EVENT REPORT	
Adverse event occurrence date	<input type="text"/> (DD MMM YYYY) *
Is this a primary or secondary event?	<input type="radio"/> Primary <input type="radio"/> Secondary* (required only for initial report) If secondary event, enter primary Adverse Event ID: <input type="text"/>
C. EVENT DESCRIPTION	
Event Category	<input type="text"/> *Help
Event Supra-term "Type of Event"	<input type="text"/> *
Event Select "Site or Modifier"	<input type="text"/> * (required only if options are present in drop down list)
Severity	<input type="text"/> *
Event Details "Description"	<input type="text"/>
Location of event treatment	<input type="text"/> Other <input type="text"/>
D. EVENT ASSESSMENT	
Expected	<input type="radio"/> Yes <input type="radio"/> No *
Causality (by reporter)	<input type="text"/> *
Was the adverse event associated with any of the following? (check all that apply)	<input type="checkbox"/> Development of a congenital anomaly or birth defect <input type="checkbox"/> Development of a permanent, serious, disabling or incapacitating condition <input type="checkbox"/> Death <input type="checkbox"/> Hospitalization or prolonged hospitalization <input type="checkbox"/> Life threatening <input type="checkbox"/> Is another condition which investigators judge to represent significant hazards
Patient status (at time of report):	<input type="text"/> *
Adverse event resolved date	<input type="text"/> (DD MMM YYYY)
Date of death	<input type="text"/> (DD MMM YYYY)
Additional comments	<input type="text"/>
E. Study Drug Activity	
Study Drug Start Date (DD MMM YYYY)	Study Drug Stop Date (DD MMM YYYY)
<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>
<input type="button" value="Add"/>	
Did the event/reaction abate after stopping drug?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Not Applicable
Did the event/reaction reappear after reintroduction?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Not Applicable
F. CONCOMITANT MEDICATIONS	
* If applicable, please ensure the concomitant medications log was updated prior to adverse event submission.	
REPORTER INFORMATION	
Reporter User ID	<input type="text"/>
<input type="button" value="Save Form"/>	<input type="button" value="Submit for Review"/>
<input type="button" value="Print"/>	<input type="button" value="Close Window"/>
Details of Initial and Previous Follow-up Reports:	

Adverse Event Reporting – Description of each field:

Section A. Interview Information:

- Adverse event report date (image 1): This section refers to the date the event was first learned. Note: This is not the date the AE Reporting Form is completed.

Initial Report	
* These fields are required in order to SAVE the form	
A. INTERVIEW INFORMATION	
Adverse event report date	(DD MMM YYYY) *

Section B. Adverse Event Report (Image 2)

- Adverse Event Occurrence date: This refers to the date on which the adverse event began.

*Note: Date **cannot** be prior to patient registration date. For treatment studies: If an adverse event occurred before participant receives first treatment, the event should not be captured on AE form. Event should be captured in Interim History Form and documented.*

B. ADVERSE EVENT REPORT	
Adverse event occurrence date	(DD MMM YYYY) *

- Is this a primary or secondary event?(Image 3):
 - A **primary** AE is the main event.
 - A **secondary** AE is not a worsening or change in severity of the primary event, but it is an AE caused by or related to the primary event. *If reporting a secondary event, the AEID of the related primary AE is entered into this field.*

For example: Participant suffers a hypoglycemia (primary event) which caused severe dizziness (secondary event).

Is this a primary or secondary event?	<input checked="" type="radio"/> Primary <input type="radio"/> Secondary* (required only for initial report) If secondary event, enter primary Adverse Event ID: <input type="text"/>
---------------------------------------	--

Section C: Event Description

- Event Category (Image 4): This refers to the body system that the AE falls under. There is a drop-down list of options. The available options depend on the body system selected under "Event Category", and are defined according to the CTCAE v3.0.

C. EVENT DESCRIPTION	
Event Category	<input type="text"/> *Help

- Event Supra-term "Type of Event" (Image 5): This refers to more specific description of the type of AE. There is a pre-populated drop-down list of the options. The drop-down list of option depends the body system selected under "Event Category", and are defined according to CTACE v3.0.

Event Supra-term "Type of Event"	<input type="text"/> *
----------------------------------	------------------------

- Event Select "Site or Modifier" (Image 6): Is further descriptor used for coding. Only required to be completed if options are present in the drop-down list.

Event Select "Site or Modifier"	<input type="text"/> * (required only if options are present in drop down list)
---------------------------------	---

- Severity: This is chosen from a pre-populated drop-down list of available options. Levels of severity are populated. Based on what is entered in Event Category and Event

Supra-term “Type of Event” options depend on the body system selected under Event Category and/or Event Supra-term and defined according to the CTCAE v3.0. Note: This does not determine if event is a serious adverse event.

Severity	*
----------	---

- **Event Details “Description”:** This section should be completed per each event. Enter a brief narrative regarding the event. Should include: Dates, Times, Places, Details, Course of Event, Interventions, and resolutions as applicable.

Note: Do not indicate PHI including gender of participant.

For Example:

Not Acceptable: “He developed a rash.”

Acceptable: “The **subject** developed a rash”

Event Details “Description”	Provide brief narrative, include dates, times, places, details, course of event, interventions and resolutions. Do Not provide any PHI information including gender.
-----------------------------	--

- **Location of Event Treatment:** Select from drop-down list: “Inpatient, outpatient, ER, none, unknown, and other”. If “other” please be sure to enter clearly the location of treatment.

Location of event treatment	Other
-----------------------------	-------

Section D: Event Assessment:

- **Expected:** Select “Yes” or “No”. Must be completed for form to be saved. Factors that determine if AE is expected:
 - If it is listed in the IB and/or ICF; or
 - If it is expected due to the type of disease under investigation.

D. EVENT ASSESSMENT	
Expected	<input checked="" type="radio"/> Yes <input type="radio"/> No *

- **Causality (by reporter):** This refers to the relatedness of the event to the investigational product (if applicable). Must be completed for form to be saved.

Causality (by reporter)	*
-------------------------	---

- **Was the adverse event associated with any of the following? (check all that apply):** This section is pre-populated with items for selection. If any of these options are selected the AE would be considered a Serious Adverse Event. *Note: AE seriousness does not relate to AE Severity.*

Was the adverse event associated with any of the following? (check all that apply)	<input type="checkbox"/> Development of a congenital anomaly or birth defect <input type="checkbox"/> Development of a permanent, serious, disabling or incapacitating condition <input type="checkbox"/> Death <input type="checkbox"/> Hospitalization or prolonged hospitalization <input type="checkbox"/> Life threatening <input type="checkbox"/> Is another condition which investigators judge to represent significant hazards
---	---

- Patient Status (at time of report): Select options from pre-populated drop down list. Must be completed for form to be saved.

Patient status (at time of report):	<div style="border: 1px solid black; height: 20px; width: 100%;"></div> <div style="text-align: right; color: red;">*</div>
-------------------------------------	---

- Adverse Event Resolved Date: Completed only if AE is resolved at time of report.

Adverse event resolved date	<div style="border: 1px solid black; height: 20px; width: 100%;"></div> <div style="text-align: right;">(DD MMM YYYY)</div>
-----------------------------	---

- Date of Death: Completed only if AE results in death. Be sure section: "Was the adverse event associated with any of the following" is completed when answering this question.

Date of death	<div style="border: 1px solid black; height: 20px; width: 100%;"></div> <div style="text-align: right;">(DD MMM YYYY)</div>
---------------	---

- Additional Comments: Add any additional pertinent information that is not captured elsewhere on the form.

Additional comments	<div style="border: 1px solid black; height: 50px; width: 100%;"></div> <div style="text-align: center; color: red; font-size: small;">Provide additional information if not captured elsewhere on the form</div>
---------------------	---

Section E. Study Drug Activity:

- Not applicable to the Pathway to Prevention study

Section F. Concomitant Medication:

- Not applicable to the Natural History/Pathway to Prevention Study

Form Disposition:

The AE can either be: Save a draft; or submit for review, print, or simply close a window.

Save Draft	Submit for Review	Print	Close Window
------------	-------------------	-------	--------------

Note: Contact TNCC CRA if there are any additional questions regarding this form

10.4 Viewing and Editing Previously Reported Adverse Events

Step 1. From the Participant's Details page, click on the Previous Adverse Events link located to the right of the PRN form dropdown box.

Completed Additional Study Forms
<ul style="list-style-type: none"> Previous Adverse Event

Step 2. The Adverse Event Form List will appear. This page lists previously reported (or previously saved but not yet reported) adverse events for this participant. If an adverse event has not yet been submitted, you will not see an Adverse Event ID (AEID) next to the event. If it has already been submitted, you will see an AEID indicated.

Step 3. Click on the blue Adverse Event ID # to view each report. You can modify a report if it was previously saved. You CANNOT modify a report which has been submitted.

Step 4.

Report a new adverse event for this participant						
Report Type	Adverse Event ID	Occurrence Date	Report Date	Primary/Secondary	Event(s)	Action
Initial	83	3/20/2009	3/23/2009	Primary	<ul style="list-style-type: none"> Allergy/Immunology - Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip) 	View Report New Follow-up

Select either View or Report New Follow-Up

Step 5. Any modifications or updates that need to be made to a previous adverse event should be submitted by completing a follow-up report. To complete a follow-up report you would select "Report New Follow-up"

10.5 Overview of Handling of Reported Adverse Events

The adverse events form will be available to investigators and delegated personnel at all study sites. As with all other aspects of TNCC-provided protocol management tools, the Adverse Events Data Management System is a secure web site with password access.

At the occurrence of an adverse event, the investigator at the local site will enter the data into the system. The Adverse Event Data Management System will immediately direct the reported information via email to the TrialNet Medical Monitor. The email contains a URL to a special website where the adverse event can be reviewed. The automated Adverse Event Data Management System forwards the adverse event information to the TrialNet Medical Monitor, who will request further information if necessary, determine causality, and possibly recommend changes to the protocol or consent form as a consequence of the adverse event. Once reviewed by the Medical Monitor, the Adverse Event Data Management System provides options to: close the adverse event case, request further/follow-up information, or request a meeting or further discussion with the TrialNet Executive Committee, DSMB, or study investigators. The Adverse Event Management System maintains audit trails and stores data (and data updates) and communication related to any adverse event in the study.

The adverse event review process described above takes place in near real-time, as the entire reporting and review is done by automatically generated emails. A back-up notification system is in place so that any delays in review beyond a specified period of time are forwarded to a secondary reviewer. Additionally, the TNCC will submit aggregate reports of all reported adverse events to the Principal Investigator and to the TrialNet DSMB to review on a periodic basis.

Adverse events from this study need to be reported to: TrialNet (medical monitor), and local IRBs for any institution where an adverse event occurs.

Local institutional reporting requirements to IRBs, any GCRC oversight committee and the FDA, if appropriate, remain the responsibility of the local site PI.

11. Protocol Manager: Portlets and Tools

From the TN01 – Pathway to Prevention homepage, there are a series of portlets meant to assist/aid sites in the conduct of the study.

11.1 TN01– Working Documents Portlet

From the TN01 – Pathway to Prevention homepage, the latest protocol related documents, manuals, and other materials to aid sites in the conduct of the study are available in the “Working Documents” portlet.

Working Documents

Current IRB Documents

[Protocol](#)
[Informed Consents](#)
[Certificate of Confidentiality](#)
[IRB Memo](#)
[DSMB Letter](#)
[Questionnaires](#)
[Volunteer Quiz](#)
[Volunteer Handbook](#)
[Recruitment Materials](#)
[Negative/Rescreen Letters](#)
[WIRB](#)
[Blood Volume Table](#)

Current Tools

[Checklists](#)
[Forms](#)
[Assessment Tools](#)
[Reimbursement Schedule](#)
[PR Materials and Incentive Items](#)
[Training Documents](#)
[New Affiliate Binder](#)

Current Manuals

[Manual of Operations](#)
[Laboratory Manuals](#)

Archive

[Previous IRB Documents](#)
[Previous Tools](#)
[Previous Manuals](#)

11.1.1 Current IRB Documents

Under the “Current IRB Documents” header are the most current versions of all protocol related documents that may need to be submitted to a site’s IRB/ethics review board.

11.1.2 Current Tools

Under the “Current Tools” header are the most current versions of all study-related materials to aid sites in the conduct of the study including:

1. Checklists
 - a. TN01 Visit Checklists
2. Forms
 - a. Participating Physician Reimbursement Forms
 - b. IRB Reimbursement Form
 - c. Lab Forms
 - i. Destruction of Samples Request Form
 - d. Eligibility Request Form
 - e. Current Site Forms
 - i. Site Information Form
 - ii. W9
 - iii. W8 (International Sites)
 - iv. Site Delegation Log
 - v. Confidentiality Agreement form
 - vi. New user Contact Form
 - f. TrialNet New Affiliate Packet.
3. Assessment Tools
 - a. CRF(s) (useful for source documentation)
 - b. Specimen Transmittal Forms (useful for source documentation).
4. Reimbursement Schedule.
5. PR Materials and Incentive Items
 - a. Branding/Logos
 - b. Printed Materials
 - c. PR Incentive Items
 - d. Presentations
 - e. Letter Templates for Families and Providers
 - f. Camp Documents
 - g. Newsletter
 - h. Press Releases.
6. Training Documents
 - a. Natural History Training Matrix
 - b. Certification Quizzes
 - c. Participating Physician/External Lab Test Kit Information
 - d. Teleform Training
 - e. Specimen Collection and Shipping.
7. New Affiliate Binder

11.1.3 Current Manuals

Under the “Current Manuals” header are the most current versions of all study-related manuals to aid sites in the conduct of the study:

1. Manual of Operations (MOO)
 - Laboratory Manuals
 - a. TN01 PTP Laboratory MOO
 - b. TN Specimen Management System MOO
 - c. TN Laboratory Specimen QC User Manual

Appendices for all manuals will be located in their respective folders:

Current Manuals Manual of Operations Laboratory Manuals
--

11.1.4 *Archive*

Under the “Archive” header are previous versions of all study-related documents for the site’s reference.

11.2 *TN01 – Actions Portlet*

From the [TN01 – Pathway to Prevention](#) homepage, all study-related actions are available in the “Actions” portlet.

Actions
Frequently Used Register a Participant Find a Participant View Test Results Prepare/Ship Specimens
Participant Data Register a Participant Find a Participant View Subject Information Portal View/Update Screening Referrals
Specimen Data View Test Results Browse Specimens Prepare/Ship Specimens Browse Prepared Shipments Browse Shipments View Shipment Reports Browse QC Collection Lists
Supplies Order Supplies
Adverse Events Medical Monitor Dashboard

11.2.1 TN01 Frequently Used

Under the “Frequently Used” actions header are links to the most often used protocol actions including:

1. Register a Participant
 - a. This link takes the user to register a new participant for the study.
2. Find a Participant
 - a. This link takes the user to locate a participant’s record.
3. View Test Results
4. Prepare/Ship Specimens.

11.2.2 Participant Data

Under the “Participant Data” actions header are links to the protocol actions that involve participant data including:

1. Register a Participant
 - a. This link takes the user to register a new participant for the study.
2. Find a Participant
 - a. This link takes the user to locate a participant’s record.
3. View Subject Information Portal (SIP)
 - a. This link takes the user to the SIP to view all subject information for their site
4. View/Update Screening Referrals

11.2.3 Specimen Data

Under the “Specimen Data” actions header are links to the protocol actions that involve specimen shipment and reports.

11.2.4 Supplies

Under the “Supplies” actions header is a link to the Supply Ordering System (SOS).

11.3 TN01– Contacts

From the [TN01 Pathway to Prevention](#) homepage, all study-related contacts are available in the “Contacts” portlet.

Contacts
Study Chair/PI Protocol Chair Email Protocol Chair
<hr/>
Coordinator Contacts
<hr/>
IRB Approved Sites
<hr/>
TNCC
TrialNet USF TNCC Contact List Email Primary CRA Email Secondary CRA

11.4 TN01– Clinical Toolkit

From the TN01 – Pathway to Prevention homepage, all study-related clinical tools are available in the “Clinical Toolkit” portlet.

Clinical Toolkit
Guidance for Fever and Illness

11.5 TN01 – Calendar

From the TN01- Pathway to Prevention homepage, all study-related calls, trainings and event are noted in the “Calendar” portlet.

TN	Protocol Name in EST
Mon Feb 27 2012	+
Tue Feb 28 2012	+
Wed Feb 29 2012	+
Thu Mar 1 2012	+
Fri Mar 2 2012	+
Sat Mar 3 2012	+
Sun Mar 4 2012	-
Monthly	

11.6 TN01 – Protocol Development Committees

From the [TN01 – Pathway to Prevention](#) homepage, links to the Protocol Chair Committee and Study Group Committee pages are located under the “Protocol Development Committee” portlet.



11.7 TN01 – Publications

From the [TN01- Pathway to Prevention](#) homepage, all protocol specific publications, ancillary publications and data sharing policies are located under the “Publications” portlet.



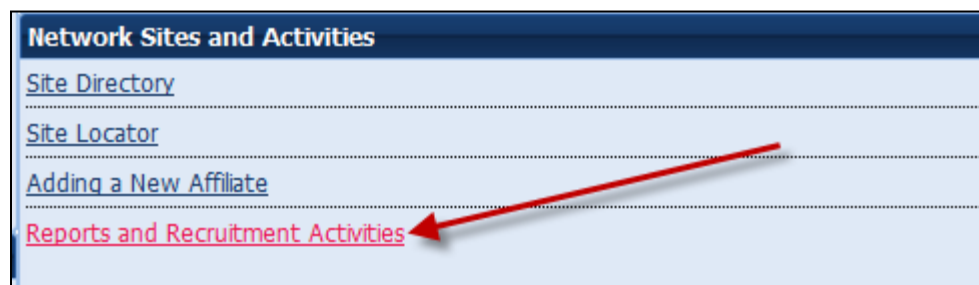
11.8 TN01– Frequently Asked Questions

From the [TN01 – Pathway to Prevention](#) homepage, all protocol specific frequently asked questions (FAQs) are located under the “Frequently Asked Questions” portlet.

12. Member’s Website Reports

12.1 Network Wide Reports

Step 2. From the main TrialNet member’s homepage, navigate to the “Network Sites and Activities” portlet. Select the “Reports and Recruitment Activities” link.



Step 2. Select your site folder.

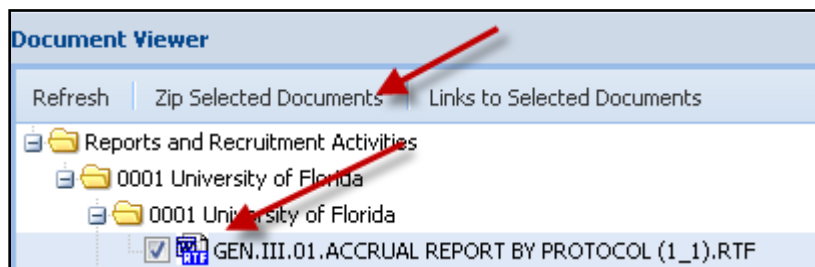
Step 3. Next, select the “General Reports” folder.

Step 4. Once you open the “General Reports” folder, you will be able to access general accrual reports for all TrialNet protocols for your clinical center and affiliate sites.

Network Wide Reports Currently Available:

Folder	Report Title	Report Description	Updated
General Reports	GEN.III.01.Accrual Report By Protocol.rtf	Displays accrual total over time.	Monthly
	GEN.II.03.IRB Expiration Report	Displays IRB expiration dates for clinical centers and affiliate sites including weeks until expiration for all TrialNet protocols	Monthly
	GEN.III.04.TrialNet Points, By Month.rtf	Displays points by month accrued by each site.	Monthly
Site Folder	GEN.III.01.Accrual Report By Protocol.rtf	Displays accrual total over time.	Monthly

Step 5. To open a report, you can click a report title to download a single report or you can select multiple reports to download by selecting the box next to each report and clicking the button “Zip Selected Documents.” This will download multiple documents to your computer as a zip file.



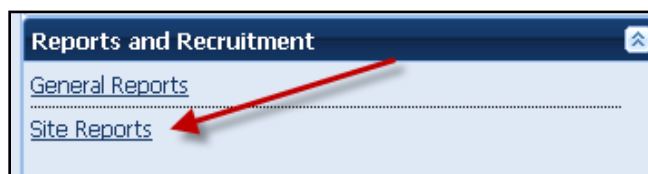
12.2 Protocol Specific Reports

From the TN01- Pathway to Prevention homepage, all general and site specific reports are located under the “Reports and Recruitment” portlet.



12.2.1 Accessing Protocol Specific Reports

Step 1. To access reports with specific data for your individual site, from the TN01 protocol page, navigate to the “Reports and Recruitment” portlet. Select the “Site Reports” link.



Step 2. Once you open the “Site Reports” folder, select your respective clinical center.

Step 3. Select the folder for your specific site.

Step 4. Once you open your site’s folder, you will have access to all protocol specific reports including accrual reports, IRB summary reports of ethnicity, race and gender, Adverse Event Summary reports, participant visit window reports and other protocol specific reports with information specific to your site.

Step 5. To open a report, you can click a report title to download a single report or you can select multiple reports to download by selecting the box next to each report and clicking the button “Zip Selected Documents.” This will download multiple documents to your computer as a zip file.

12.2.2 Protocol Specific Reports Currently Available:

Folder	Report Title	Report Description	Updated
General Reports	TN01.01.NHS Screening and Enrollment Report.rtf	Accrual totals, network wide	Weekly
	TN01.I.01. Accrual Report by Clinical Center.rtf	Accrual totals, by clinical center	Monthly
	TN01.I.02.Actual.v.Expected Accrual - Graph.rtf	Graph of actual verses expected accrual.	Monthly
	TN01.II.03.IRB Summary - Ethnicity, Race and Gender Report.rtf	IRB summary of ethnicity, race and gender for all subjects	Monthly
	TN01.I.04.Adverse Event Summary Report.rtf	Summary of all reported AEs and SAEs	Weekly

Site Reports	TN01.II.01.Accrual Report By Institution (CC#).rtf	Accrual summary for clinical center and all affiliates	Monthly
	TN01.II.02.IRB Summary - Ethnicity, Race and Gender Report (CC#).rtf	IRB summary of ethnicity, race and gender for each site	Monthly
	TN01.II.11.List of Potential TN07 Participants (CC#).rtf	Potentially eligible participants for TN07 by site	Daily
	TN01.II.02.Participants with an Initial BAA Positive Sample (CC#).rtf	Initial BAA positive participants by site	Daily
	TN01.II.02.List of Participants Eligible for TN10 (CC#).rtf	Eligible participants for TN10 by site	Daily
	TN01.II.02.List of TN01 Participants Potentially Eligible for TN10 (CC#).rtf	Potentially eligible participants for TN10 by site	Daily
	TN01.III.01.Accrual Report (CC#_Site#).rtf	Displays protocol accrual totals	Monthly
	TN01.III.02.IRB Summary - Ethnicity, Race and Gender Report (CC#_Site#).rtf	Displays IRB summary of ethnicity, race and gender	Monthly
	TN01.III.03.Adverse Event Summary Report (CC#_Site#).rtf	Displays summary of all AEs and SAEs	Monthly
	TN01.III.09.Participant Schedule of Visits Report (CC#_Site #).rtf	Displays a calendar of target dates for subjects' visits	Daily
	TN01.II.01.List of Potential TN07 Participants (CC#_Site #).rtf	Displays potentially eligible participants for TN07	Daily
	TN01.II.12.Participants with an Initial BAA Positive Sample (CC#_Site #).rtf	Displays initial BAA positive participants	Daily
	TN01.II.16.Screening Report by Month (CC#_Site##).rtf	Displays all screening reports by year and month	Daily
	TN01.III.17.Follow-Up of Eligible Participant Form (CC#_Site #).rtf	Displays all Follow-Up of Eligible Participant Forms completed	Monthly

13. SUPPLIES

13.1 Supply Ordering System Overview

All TrialNet supplies are ordered by sites through the Fisher BioServices online Supply Ordering System. This includes specimen collection, processing, and shipping supplies, barcode scanners, subject questionnaires, diabetes management supplies, and recruitment and retention materials. Supplies are shipped by three primary vendors: Fisher BioServices, TradeWinds, and the TNCC:

- **Fisher BioServices** – collection tubes, barcode labels, clinical supplies, specimen processing and shipping supplies
- **TradeWinds** – etched shipment vials
- **TNCC** – lifestyle questionnaires, scheduling wheels, TN01 teleforms, recruitment and retention materials, diabetes management supplies (if applicable).

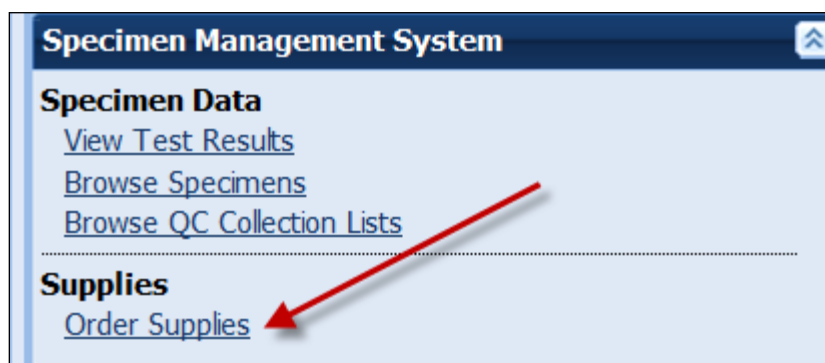
The TNCC reviews and approves all orders placed in the Fisher online system within 48 hours and, if applicable, contacts TradeWinds to fulfill etched vial orders. Some supplies are directly supplied by the USF TNCC, including lifestyle questionnaires, scheduling wheels, teleforms, and recruitment materials.

13.2 Ordering Supplies

13.2.1 Navigating the Fisher BioServices Supply Ordering System (SOS)

Step 1. There are multiple ways to access the online Supply Ordering System.

From the members website main page, navigate to the “Specimen Management System” portlet on the left hand side of the page and select “Order Supplies.”



From the Pathway to Prevention Study homepage, navigate to the central “Actions” portlet and select “Order Supplies.”

Actions
Frequently Used Register a Participant Find a Participant View Test Results Prepare/Ship Specimens
Participant Data Register a Participant Find a Participant View Subject Information Portal View/Update Screening Referrals
Specimen Data View Test Results Browse Specimens Prepare/Ship Specimens Browse Prepared Shipments Browse Shipments View Shipment Reports Browse QC Collection Lists
Supplies Order Supplies
Adverse Events AE Admin External AE Reporting

Step 2. The Supply Ordering System (SOS) web page will appear in a new window. You will be prompted to enter your TrialNet Supply Order System Login information.

Note: If you do not have a login, please contact the TNCC to obtain a user account.

User ID:	<input type="text"/>
Password:	<input type="password"/>
<input type="button" value="Login"/>	
Provided by  Fisher BioServices	

Step 3. Select "Add New Supply Order." You may also view a complete list of supplies.

Add New Supply Order
View All Supplies

- Step 4. Enter the date you need the order to arrive at your site by and select “Proceed.”
Please allow at least 3-4 weeks for delivery on most items.

Please choose the date that you need this order to arrive at the site (mm/dd/yyyy):

←

Click to
Display a
Calendar

Proceed
View Holiday Schedule for 2012
Cancel

* Please note that processing of an order cannot begin until the order is approved.

There are no pending holidays that the supply provider, Fisher BioServices, observes for the remainder of this month (July).

- Step 5. After entering the date and selecting “Proceed” you will be prompted to confirm the date and either select proceed or opt to re-enter the date. If the date you have selected is OK, please select “Yes, Proceed with Order.” If not then select “No, Re-Enter Date Required at Site.”

The 'Site Arrival Date' that was entered is Wednesday, 08/22/2012, and it is 48 calendar days away from now (the total number of business days until this date is 34).

Are you sure this is correct?

Yes, Proceed with Order
No, Re-Enter Date Required at Site

- Step 6. Once you have confirmed the date is correct and selected “Yes, Proceed with Order” you will be prompted to enter order instructions or comments OR proceed to the order without special instructions:
- a. If you would like to enter special instructions, please enter them into the box provided and select “Save Special Instructions/Comments and Proceed to Supply Order.”
 - b. If you do not have any special instructions or comments regarding the order, please select “Skip instructions/Comments Entry and Proceed to Supply Order.”

Order # 18476

[Delete Order](#)

If any of the following options apply for this order, please check-off the appropriate checkboxes:

☐ Specialized Container and/or Packing Required.
☐ Temperature Monitor Required.
☐ Specific Documentation Needs to be Enclosed *(Please elaborate below)*.
☐ Special Labeling Required *(Please elaborate below)*.
☐ Infectious Shipment.

Required Site Arrival Time HHMM *(Optional)*: Purchase Order Number *(Optional)*:

Order Instructions/Comments (i.e. Anything pertinent the order fulfillers should know) :

Important! Please do not use this section as the place to specify the shipping site. The site must either be registered already or manually entered later in this process when the site is to be chosen. Otherwise, your order may not be queued properly.

1 → [Acknowledge Shipping Site Warning](#)

Do NOT use this space to specify the shipping site destination. Choosing the site is done later. Click the above "Acknowledge Shipping Site Warning" button to acknowledge this important warning.

[Save Special Instructions/Comments and Proceed to Supply Order](#)
OR
[Skip Instructions/Comments Entry and Proceed to Supply Order](#)

Important! Please do not use this section as the place to specify the shipping site. The site must either be registered already or manually entered later in this process when the site is to be chosen. Otherwise, your order may not be queued properly.

[Acknowledge Shipping Site Warning](#)

2 →

After Shipping Site Warning is acknowledged, the text box and "Proceed to Supply Order" buttons are enabled. You may enter special instructions (if required) and save **OR** proceed to supply order without entering instructions.

[Save Special Instructions/Comments and Proceed to Supply Order](#)
OR
[Skip Instructions/Comments Entry and Proceed to Supply Order](#)

Step 7. Enter the "Ship to Site" by selecting a site from the "Ship-To" dropdown menu.

[Abandon/Delete Order](#)

Anticipated Ship Date: 08/20/2012 (Monday) / Site Arrival Date: 08/22/2012 (Wednesday)

[Finished Entering Items - Click Here to Continue](#)

[Sort by Site ID](#) **Ship-To:** TNCC (S000PEC — Kelly Sadler)

Contact: [Kelly Sadler](#)

2 →

S000PEC - TNCC - Kelly Sadler
University of South Florida
USF Pediatrics Epidemiology Center
3650 Spectrum Blvd, Suite 100
Tampa, FL 33612 USA

1

Step 8. Select the Protocol/Study and Assay for which you want to order supplies.

Select a Protocol/Study	Select Assay
Select a Protocol	Select Assay
Select a Protocol General TN05 Anti-CD20 TN07 - Oral Ins (North American Sites) TN09 CTLA-4 Ig TN08 GAD New Onset TN07 - Oral Ins (International) TN14 Anti-IL1 Beta TN10 Anti-CD3 Prevention TN01 PTP Monitoring (International Sites) TN01 PTP Monitoring (North American Sites) TN01 PTP Screening (North American Sites) TN01 PTP Screening (International Sites)	

If you wish to order general supplies, please select “General” for the Protocol/Study. Under the Secondary Filter Criteria, sites may select from clinical supplies, PBMC isolation supplies (applicable to TN07 only), PR incentive items, questionnaires, and shipping supplies.

Select a Protocol/Study	Select a Secondary Filter Criteria
General	Select Assay
	Select Assay Clinical Supplies PBMC Isolation - Ficoll (TN07) PR Incentive Questionnaires Shipping

Step 9. Once a Protocol and Assay are selected, the window will refresh and the applicable supplies will populate below.

Select a Protocol/Study				Select Assay			
TN01 PTP Monitoring (North American Sites) ▾				Autoantibodies ▾			

Item #	Item Description	Part #	Catalog #	Packaging Unit Explanation	Packaging Units	Units Ordered	Total Quantity Ordered	Threshold Limit	Expiration Date	Provider	Selected
TWDred1.8	1.8 mL Red Top Shipment Cryovial - Etched		BD 368632	Explain	50	<input type="text"/>	0	0		USF	<input type="checkbox"/>
PR-00042	2.6 mL Gold Top SST Collection Tube		04.1905.001 & NC9363630	Explain	50	<input type="text"/>	0	0	31-Mar-2013	Fisher BioServices	<input type="checkbox"/>

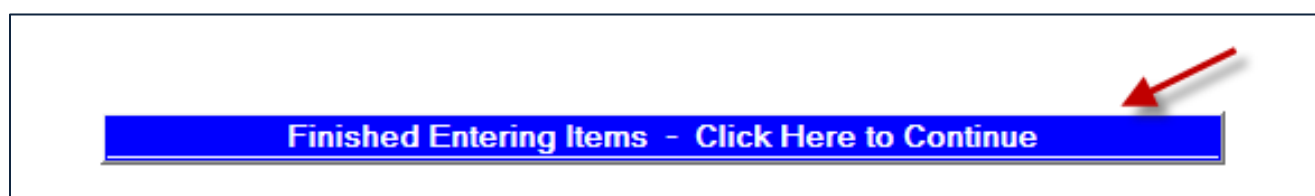
Step 10. Select the supplies you wish to order by placing a checkmark in the “Selected” column and indicating the number of units desired. Please note the packaging units per item when entering the number of units you require. Some items are

packaged individually (Packaging Units = 1), while other supplies come in larger quantities. The “Total Quantity Ordered” field will update to reflect the total number of items that will be shipped.

For example, 1 unit of the 8.0 mL shipment tubes contains 50 tubes. Since 2 units were ordered below, a total of 100 tubes will be shipped.

Item #	Item Description	Part #	Catalog #	Packaging Unit Explanation	Packaging Units	Units Ordered	Total Quantity Ordered	Threshold Limit	Expiration Date	Provider	Selected
TWD8.0	8.0 mL Polypropylene Shipment Tube - Etched		BD 368632	Explain	50	2	100	0		USF	<input checked="" type="checkbox"/>
PR-00133	8.5 mL Red/Gray Top SST Collection Tube	02-683-96	367988 & 02-683-96	Explain	100	1	100	0	30-Apr-2013	Fisher BioServices	<input checked="" type="checkbox"/>

Step 11. Once your order is complete, click on the blue “Finished Entering Items” tab at the top of the page.



Step 12. The order summary will now appear on the page. Please confirm the address and contact information in the order summary is correct. Once you confirm the address and order summary is correct, click on the “Submit” tab to submit your order.

ORDER FORM SUMMARY (ORDER NUMBER: 17400)

[Return to Home Page](#)
[Add More Items](#)
[Update Units Ordered](#)
[Add Comment](#)
[Submit Order](#)

[Generate Template of the Order Items Below for Future Orders](#)
[Display Printer Friendly Order View](#)
[OK](#)

If you have any questions regarding the status of your order or if you encounter any problems placing an order, please contact the TNCC.

13.2.2 Supply Organization

Supplies are organized on the Fisher BioServices online Supply Ordering System (SOS) website by “Protocol” and by “Test/Assay.” For each user, access to a protocol is granted based on the center’s Site Delegation Log.

In order to view and order supplies, users must first select a “Protocol” and then select a “Test/Assay” from the dropdown menus (see Section 12.1.1, Step 8).

The TN01 Pathway to Prevention Study is divided into four “protocols” based upon study phase (Screening vs. Monitoring) and site location (North America vs. International). Each of the 4 protocol listings contain only the tests applicable to that study phase and site location. Specimen collection and shipment tubes and/or vials are listed under each assay heading.

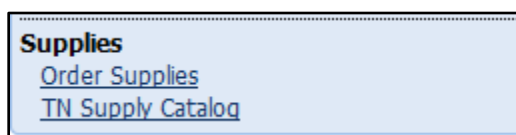
All other supplies are listed under “General” in the “Protocol” filter. For general supplies, the “Test/Assay” secondary filter refers to the major item category: clinical, shipping, PR incentive, and questionnaires.

The table below lists all filter criteria applicable to the TN01 Pathway to Prevention Study. Please refer to Appendix? for a complete list of items available for the TN01 Pathway to Prevention Study.

Of note, specimen barcode scanners are now posted under General Clinical supplies.

TN01 Pathway to Prevention Supply Organization	
“Protocol” Filter Criteria	“Test/Assay” Secondary Filter Criteria
TN01 PTP Screening (North American Sites)	Autoantibodies
TN01 PTP Screening (International Sites)	Autoantibodies
TN01 PTP Monitoring (North American Sites)	Autoantibodies HbA1c HLA Whole Blood - PBMC/Plasma Whole Blood - RNA Mechanistic Serum Questionnaires
TN01 PTP Monitoring (International Sites)	Autoantibodies HbA1c HLA Whole Blood - RNA Mechanistic Serum
General Supplies	Clinical Shipping PR Incentive Questionnaires

To access the TrialNet Supply Catalogue, you can find the following link on the TrialNet Member’s Website home page:



14. TNCC Audit Program

14.1 Selection of Institutions/Investigators

14.1.1 Observational Studies

TrialNet will not audit observational studies except on a for-cause basis.