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Protocol TN16
Long Term Investigative Follow-up in TrialNet (LIFT)

Dr. Jennifer Marks

Manual of Operations
Version 13MAR2015

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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:

1. 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.
2. 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 (Version Date 12FEB2015)

Title	Long-Term Investigative Follow-Up in TrialNet (LIFT)
Conducted By	Type 1 Diabetes TrialNet
Protocol Chair	Jennifer B. Marks, MD
Study Design	This is a descriptive study to evaluate the Long-Term effects of participation in TrialNet studies.
Study Duration	Subjects will be followed indefinitely
Major Inclusion Criteria	1. Type 1 Diabetes 2. Prior to participation in TrialNet 3. Willing to give, informed consent / assent (as applicable for children)

1.3 Study Contacts

TN16 LIFT Study TrialNet Coordinating Center (TNCC)		
USF TrialNet Coordinating Center (TNCC) University of South Florida Pediatrics Epidemiology Center Tampa, FL 33615	Primary Contact: Mary Deemer	Ph.: (813) 396-9113 Fax: 813-910-1229 Email: Mary.Deemer@epi.usf.edu
	Secondary Contact: Joy Ramiro	Ph.: ((813) 396-9211 Fax: (813) 910-5976 Email: Joy.Ramiro@epi.usf.edu

TN16 LIFT Study Core Laboratories
Please refer to the TN16 LIFT Laboratory Manual for a complete list of TrialNet Core laboratories applicable to the TN16 protocol.

For participating site contact information please refer to TN16 Contact Portlet located on the bottom of the protocol homepage of the members website.

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:

1. 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.
2. 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.
3. Ensure that all site investigators and research staff are appropriately qualified and fully aware of their obligations.
4. Ensuring local site initial and continuing Institutional Review Board (IRB)/Ethics Committee review and approval of the protocol (amendments, changes, updates, etc.).

5. Review local site adverse events (AEs) and ensure that AEs have been addressed appropriately and reported correctly.
6. Supervise the preparation of training materials and procedure manuals at the site.
7. Review all trial and patient care issues that occur at the local site.
8. 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. 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).

3.2 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.

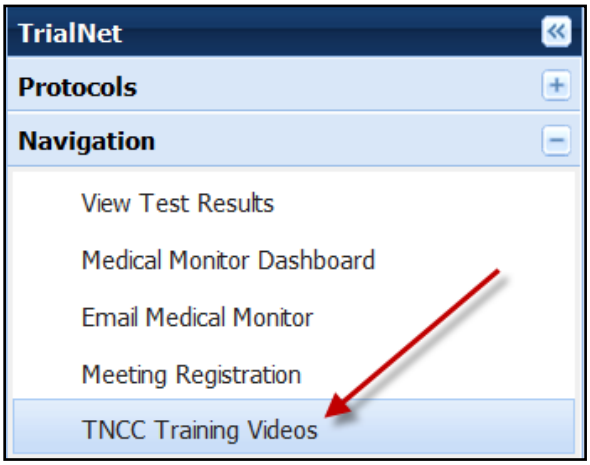
3.4 Study/System Training

Each site is required to have at least one person trained on the protocol and online system at all times.

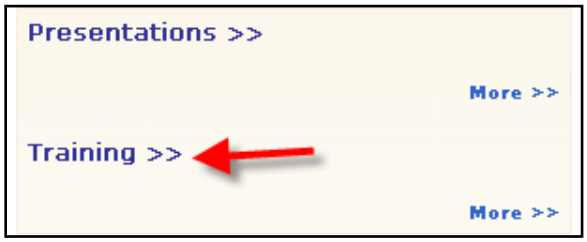
3.4.1 Online Training

Demonstration and training videos are available online. **You must have <u>Windows Media Player</u>** 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.

Title	Date
Protocol Training – TN16 Long-Term Investigative Follow Up in TrialNet (LIFT)	September 2012
TrialNet ADA Affiliate Meeting Presentation	June 2011
Protocol Training - TN14 Anti IL-1Beta	September 2010
Protocol Training - TN10 Anti-CD3 Prevention	August 2010
TrialNet Training – Harmonized Assay Adoption	May 2010
TrialNet Training - General Members Website	March 2009
Protocol Training – TN01 Pathway To Prevention	March 2009
Protocol Training – TN05 Anti CD20	March 2009
Protocol Training – TN07 Oral Insulin	March 2009
Protocol Training – TN08 GAD Intervention	March 2009

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

Protocol Training – TN16 Long-Term Investigative Follow Up in TrialNet (LIFT)

Original Release Date: 9/10/2012

Date of Expiration: 9/10/2014

Target Audience: This program is intended for members of the Type 1 Diabetes TrialNet

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

Title	Speaker	Date
TN16 LIFT Protocol Overview	Jennifer B. Marks M.D.	9/10/2012
TN16 LIFT Groups, Visits, and Procedures	Joy Ramiro	9/7/2012
TN16 LIFT On-line Participant Registration	Joy Ramiro	8/30/2012
TN16 LIFT Reporting of Adverse Events	Joy Ramiro	8/28/2012

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. TN16 Protocol Overview: Provides a description of the protocol, eligibility criteria, purpose, specific aims, and details of procedures.
2. TN16 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.

3.5 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.

3.6 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:

3.6.1 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).

3.6.2 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.

3.6.3 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.

3.6.4 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.
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 3.7.2).

3.6.5 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
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 3.7.2).

3.6.6 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.

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 a *maximum 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.

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.
- Randomization occurs via the protocol manager (online data capture system)
- 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 and- of those- total number randomized.
- Recruitment reports and efforts will be monitored by the TNCC, study chair, and discussed by the study committee

4.3 Eligibility Criteria

Inclusion Criteria:

- Type 1 Diabetes and was Diagnosed with Type 1 Diabetes as of August 1, 2012 moving forward.
- Prior participation in a TrialNet study.
- Willing to give, informed consent/assent (as applicable for children).

Exclusion Criteria:

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

4.4 Exceptions to Questions Regarding Eligibility Criteria

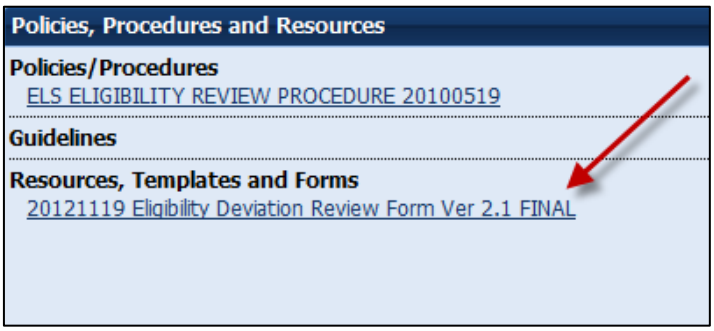
The TrialNet Coordinating Center will be responsible for initially reviewing and adjudicating any instances where eligibility is unclear. If following this initial review eligibility is still unclear, the TrialNet Eligibility Committee will review and adjudicate the situation.

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. (Refer to Appendix U).

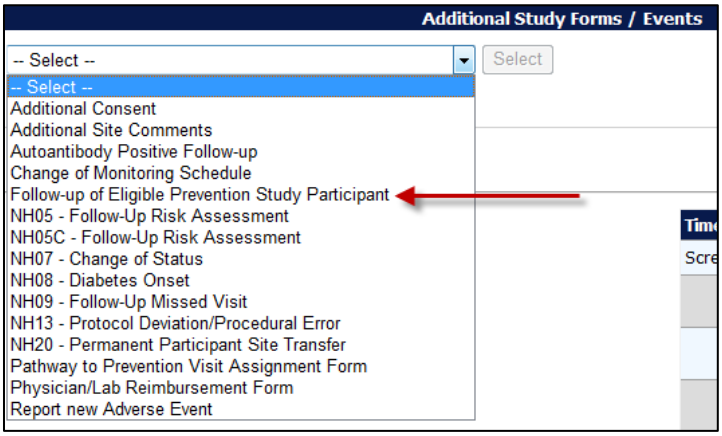
Step 4. Once a decision has been made by the Eligibility Deviation Review Committee a copy will be provided to the site. It should be initialed, dated and placed with your source documents.

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. (*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 Participant Details page.



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. *(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
☐ Conflicting Responsibilities (Work, School, Family)	○ 1 Very Important ○ 2 Important ○ 3 Somewhat Important
☐ Time Commitment	○ 1 Very Important ○ 2 Important ○ 3 Somewhat Important
☐ 2 week Infusion Period	○ 1 Very Important ○ 2 Important ○ 3 Somewhat Important
☐ Unable/ Unwilling to Travel	○ 1 Very Important ○ 2 Important ○ 3 Somewhat Important
☐ Participant does not tolerate OGTT/IVGTTs well	○ 1 Very Important ○ 2 Important ○ 3 Somewhat Important
☐ Fear of Study Drug Risks	○ 1 Very Important ○ 2 Important ○ 3 Somewhat Important
☐ Concerns about receiving placebo	○ 1 Very Important ○ 2 Important ○ 3 Somewhat Important
☐ Family wishes to wait until participant is older	○ 1 Very Important ○ 2 Important ○ 3 Somewhat Important
☐ Does not want to be blinded to individual test results during the study	○ 1 Very Important ○ 2 Important ○ 3 Somewhat Important
☐ Unwilling to take investigational drug	○ 1 Very Important ○ 2 Important ○ 3 Somewhat Important
☐ Pregnant, nursing or planning children in the future	○ 1 Very Important ○ 2 Important ○ 3 Somewhat Important
☐ Monetary Compensation	○ 1 Very Important ○ 2 Important ○ 3 Somewhat Important
☐ Other	○ 1 Very Important ○ 2 Important ○ 3 Somewhat Important
☐ Refused; no reason given	○ 1 Very Important ○ 2 Important ○ 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 TN16 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 TN16 Laboratory Manual of Operations.

Notes:

- Refer to Appendices C and G for Flowcharts, Completion and/or Combination Procedure Instructions.
- Refer to Appendices H thru K for Tolerance Test Procedures, Tolerance Test Checklist, and Tolerance Test Carohydrate Menu.

5.1 Initial Visit

Visit Windows:

- Group 1: Participants from TN01 Pathway to Prevention or any of the TN prevention studies who are newly diagnosed with Type 1 diabetes.The initial visit window will be 2 months (+/- 4 weeks) after date of diagnosis.

- Group 2: Participants already diagnosed with Type 1 diabetes and are from any of the TN New Onset studies.The initial visit window can occur at anytime.

Time Point	Description of Procedure	Source Document	eCRFs
Pre-Visit	Complete the online Registration	NA	Registration Form
	Review the 'Initial Visit Checklist' and ensure site is prepared for the visit. *Checklist is available online.* Remind the participant they should fast for the tolerance test if performed. *Refer to appendix I for Tolerance Test Preparation Checklist*.	NA	NA
	Scan barcodes for each central laboratory specimen 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	Initial Visit Specimen Collection
At Visit	Administer the consent (and assent if participant is under the age of 18).	Consent and/ or Assent	NA
	Confirm Eligibility	Initial Visit Assessment Tool	Eligibility
	Assess and collect from the participant: General health Directed physical exam, including weight and height. Diabetes Management	Initial Visit Assessment Tool	Diabetes and Health Information
	Ask the participant about any current	Concomitant Medications	Concomitant Medications

	medications. *Do not complete concomitant medications form if the participant reports they are not taking medication.*		
	Report an adverse event in the source document if it's related to the TN16 LIFT study procedures. (*Complete eCRF if SAE*).	AE assessment	Adverse Events
	Initial lab collection(s): 4. Whole Blood – HbA1c 5. Tolerance Test – OGTT or 2 HR MMTT Group 1 (TN01 PTP or any prevention studies) collect OGTT. Group 2 (TN New Onset studies) collect 2 HR MMTT. *Do NOT collect MMTT if last MMTT result is non-detectable C-peptide.* 6. Mechanistic Specimens a. Whole Blood – PBMC/Plasma *(North American sites only)* b. Whole Blood – RNA c. Serum – Mechanistic Serum	HbA1c Assessment Tool OGTT and/or MMTT Assessment Tool(s) Mechanistic Specimen Assessment Tool Signed and dated printout of specimen collection form	Initial Visit Specimen Collection Diabetes and Health Information

Post Visit	Enter data collected on source documents into the eCRFs.
	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system. *Be sure to compare printed shipment manifest to specimens prior to shipment*
	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.
	Review 'Initial Visit' MMTT results under 'View Test Results' to determine if Group 2 participants will continue onto semi-annual or annual visits. Group 1 participants will continue to the 6 Month visit regardless of C-peptide result.

** Barcodes may be scanned prior to, during, or after the visit which depends on site workflow.*

5.2 6 Months

Visit Window: +/- 6 Weeks

Time Point	Description of Procedure	Source Document	eCRFs
Pre-Visit	Review the '6 Month Visit Checklist' and ensure site is prepared for the visit. *Checklist is available online.* Remind the participant that they should fast for the tolerance test if performed and **this is a 2**	NA	NA

	day visit for those in Group 1. *Refer to appendix I for Tolerance Test Preparation Checklist.*		
	Scan barcodes for each central laboratory specimen 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	Specimen Collection
At Visit	Assess and collect from the participant: General health Directed physical exam, including weight and height. Diabetes Management	Follow-Up Assessment Tool	Diabetes and Health Information
	Ask the participant about any current medications. *Do not complete concomitant medications form if the participant reports they are not taking medication.*	Concomitant Medications	Concomitant Medications
	Report an adverse event in the source document if it's <u>related</u> to the TN16 LIFT study procedures. (*Complete eCRF if SAE*).	AE assessment	Adverse Events
	6 Month lab collection(s): 7. Whole Blood – HbA1c 8. Tolerance Test(s) – OGTT and/or 2 HR MMTT <u>Group 1</u> (TN01 PTP or any prevention studies) Day 1 collect OGTT Day 2 collect 2 HR MMTT *This is a 2 day visit with OGTT as the priority if only one tolerance test is collected.* <u>Group 2</u> (TN New Onset studies) Collect 2 HR MMTT if Initial visit MMTT result is detectable for C-Peptide. Do NOT collect MMTT if Initial Visit MMTT result is non-detectable for C-Peptide. (*Select 'Not Required' on specimen collection form*). 9. Mechanistic Specimens	HbA1c Assessment Tool OGTT and/or MMTT Assessment Tool(s) Mechanistic Specimen Assessment Tool Signed and dated printout of specimen collection form	Specimen Collection Diabetes and Health Information

	a. Whole Blood – PBMC/Plasma *(North American sites only)* b. Whole Blood – RNA c. Serum – Mechanistic Serum		

Post Visit	Enter data collected on source documents into the eCRFs.
	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system. *(Be sure to compare printed shipment manifest to specimens prior to shipment)*
	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.
	Review '6 Month' MMTT results under 'View Test Results' to determine if Group 2 participant will continue on semi-annual or annual visits. Group 1 participants will continue to the 12 Month visit regardless of C-peptide result.

** Barcodes may be scanned prior to, during, or after the visit which depends on site workflow.*

5.3 12 Months(One Year):

Visit Window: +/- 6 weeks

Time Point	Description of Procedure	Source Document	eCRFs
Pre-Visit	Review the '12 Month Visit Checklist' and ensure site is prepared for the visit. *Checklist is available online.* Remind the participant that they should fast for the tolerance test if performed and **this is a 2 day visit for those in Group 1**. *Refer to appendix I for Tolerance Test Preparation Checklist*.	NA	NA
	Scan barcodes for each central laboratory specimen 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	Specimen Collection
At Visit	Assess and collect from the participant General health Directed physical exam, including weight and height. Diabetes Management	Follow-Up Assessment Tool	Diabetes and Health Information
	Ask the participant about any current medications. *Do not complete concomitant*	Concomitant Medications	Concomitant Medications

	medications form if participant reports they are not taking any medications.		
	Report an adverse event in the source document if it's <u>related</u> to the TN16 LIFT study procedures. (*Complete eCRF if SAE*).	AE assessment	Adverse Events
	12 Month lab collection(s): 1. Whole Blood – HbA1c 2. Tolerance Test(s) – OGTT and/or 2 HR MMTT <u>Group 1</u> (TN01 PTP or any prevention studies) *Participants that are entering the study for the first time 12 months (+/- 6 weeks) since their T1D diagnosis will start at the 12 month visit.* Day 1 collect 2 HR MMTT Day 2 collect OGTT *This is a 2 day visit with MMTT as the priority if only one tolerance test is collected.* <u>Group 2</u> (TN New Onset studies) Collect 2 HR MMTT if 6 Month MMTT result is detectable for C-peptide. Do NOT Collect 2 HR MMTT if 6 Month MMTT result is non-detectable for C-Peptide. *(Select 'Not Required' on specimen collection form).* 3. Mechanistic Specimens a. Whole Blood – PBMC/Plasma *(North American sites only)* b. Whole Blood – RNA c. Serum – Mechanistic Serum	HbA1c Assessment Tool OGTT and/or MMTT Assessment Tool(s) Mechanistic Specimen Assessment Tool Signed and dated printout of specimen collection form	Specimen Collection Diabetes and Health Information

Post Visit	Enter data collected on source documents into the e-CRFs online.
	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system. *(Be sure to compare printed shipment manifest to specimens prior to shipment)*
	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.
	Review '12 Month' MMTT results under 'View Test Results' to determine if Groups 1 or 2 participants will continue on semi-annual or annual visits.

5.4 Semi-Annual Visits (Months 18, 24, 30, 36… etc)

For participants who continue to produce c-peptide only.

Visit Window: +/- 6 Weeks

Time Point	Description of Procedure	Source Document	eCRFs
Pre-Visit	Review the 'Semi-Annual Visit Checklist' and ensure site is prepared for the visit. *Checklist is available online.* Remind the participant that they should fast for the tolerance test if performed. *Refer to appendix I for Tolerance Test Preparation Checklist.*	NA	NA
	Scan barcodes for each central laboratory specimen 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	Specimen Collection
At Visit	Assess and collect from the participant: General health Directed physical exam, including weight and height. Diabetes Management	Follow-Up Assessment Tool	Diabetes and Health Information
	Ask the participant about any current medications. *Do not complete concomitant medications form if the participant reports they are not taking medications.*	Concomitant Medications	Concomitant Medications
	Report an adverse event in the source document if it's <u>related</u> to the TN16 LIFT study procedures. (*Complete eCRF if SAE*).	AE assessment	Adverse Events
	Visit lab collection(s): 10. Whole Blood – HbA1c 11. Tolerance Test – 2 HR MMTT <u>Group 1</u> (TN01 PTP or any prevention studies) *Participants that are entering the study for the first time 12 months (+/- 6 weeks) since their T1D diagnosis will start at the 12 month visit.* <u>Group 2</u> (TN New Onset Studies) Collect 2 HR MMTT if previous MMTT result is	HbA1c Assessment Tool MMTT Assessment Tool Mechanistic Specimen Assessment Tool Signed and dated printout of specimen	Specimen Collection Diabetes and Health Information

	detectable for C-Peptide 12. Mechanistic Specimens a. Whole Blood – PBMC/Plasma *(North American sites only)* b. Whole Blood – RNA c. Serum – Mechanistic Serum	collection form	

Post Visit	Enter data collected on source documents into the e-CRFs online.
	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system. *(Be sure to compare printed shipment manifest to specimens prior to shipment)*
	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.
	Review MMTT results under 'View Test Results' to determine if participant will continue on semi-annual or annual visits.

** Barcodes may be scanned prior to, during, or after the visit which depends on site workflow.*

5.5 Annual Visits (Months 12, 24, 36, 48… END)

For participants whose MMTT result no longer has detectable c-peptide.
Visit Window: +/- 6 Weeks

Time Point	Description of Procedure	Source Document	eCRFs
Pre-Visit	Review the 'Annual Visit Checklist' and ensure site is prepared for the visit. *Checklist is available online.*	NA	NA
	Scan barcodes for each central laboratory specimen 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	Specimen Collection
At Visit	Assess and collect from the participant: General health Directed physical exam, including weight and height. Diabetes Management	Follow-Up Assessment Tool	Diabetes and Health Information
	Ask the participant about any current medications. *Do not complete concomitant medications form if the participant reports they are not taking any medications.*	Concomitant Medications	Concomitant Medications
	Report an adverse event in the source document if it's <u>related</u> to the TN16 LIFT study	AE assessment	Adverse Events

	procedures. (*Complete eCRF if SAE*).		
	Visit lab collection(s): Group 1 (TN01 PTP or any prevention studies) and Group 2 (TN New Onset Studies) 13. Whole Blood – HbA1c 14. Mechanistic Specimens a. Whole Blood – PBMC/Plasma *(North American sites only)* b. Whole Blood – RNA c. Serum – Mechanistic Serum	HbA1c Assessment Tool Mechanistic Specimen Assessment Tool Signed and dated printout of specimen collection form	Specimen Collection Diabetes and Health Information

Post Visit	Enter data collected on source documents into the e-CRFs online.
	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system. *(Be sure to compare printed shipment manifest to specimens prior to shipment)*
	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.

** Barcodes may be scanned prior to, during, or after the visit which depends on site workflow.*

5.6 End of Study Participation

5.6.1 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.

5.6.2 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 “Change of 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-CRF’s 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 “Change of 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).

5.6.3 Participant – Determining Lost to Follow Up

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

Step 1. Contact the participant by phone, email, or regular mail.

Step 2. Note date and how participant is contacted in the source document.

Step 3. If no response after third try, send a certified letter to the participant.

Step 4. If still no response after the certified letter was sent, review with PI and deem participant "Lost to Follow Up."

5.6.4 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.

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

5.6.5 Death

All deaths are considered serious adverse events if related to TN16 LIFT study procedure and should be reported within 24 hours of notification, as this is an unexpected event for participants in the Oral Insulin Study. Sitecoordinators should follow these procedures:

1. Report an adverse event for the incident within 24 hours of notification.
2. Complete "Mortality Event Form" in the online data capture system. Complete this form regardless of the cause of death.
3. Complete a "Change of Status Form" in the online data capture system indicating the participant is becoming inactive.
4. Complete a "Change in Study Drug Form" in the online data capture system indicating the participant is discontinuing study medication.
5. Send a copy of the death certificate (if/when available) to the TNCC.

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. Notify the originating site pharmacy of the transfer if the participant has not completed the course of treatment. The originating site should contact the TNCC for additional steps regarding transfer of study agent.

Step 7. 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 "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 8. 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 (Physician's Office/External Laboratory)

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.

Definitions:

The **unapproved site** refers to the site that is not approved under the 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 which the participant is currently enrolled.

A **study visit** is defined as all those procedures associated with a particular visit which includes, but is not limited to:

- Specimen collection
- Physical examination
- Adverse event assessment

A **specimen collection visit** is defined as follows:

- Collection of specimen ONLY
- NO physical examination
- NO assessment of adverse events*
  - Study coordinator at the enrolling site may call the participant to assess adverse events but the unapproved site/physican's offce should NOT assess adverse events.

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 enrolling site will provide the study kit to the participant.

a. Refer to Appendices O thru T for HbA1c remote collection instructions. Instructions divided by the following:
   - Instructions for Lab for Physician's Office or Non-Quest Lab
   - Instructions for Site for Physicians's Office or Non-Quest lab
   - Instructions for Lab for Quest Diagnostic Lab
   - Instructions for Site for Quest Diagnostic Lab

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.

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.

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.

7.2 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

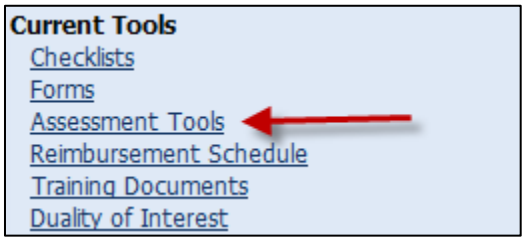
7.2.2 Documentation of the Informed Consent Process

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:

1. 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.

2. 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 TN16 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

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 logins 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 logins 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.

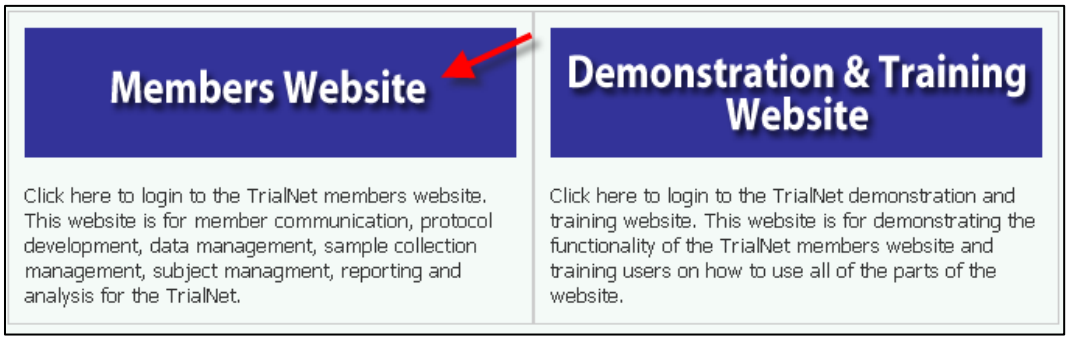
Registration of participants on this protocol employs an interactive data system in which the clinical site will attest to the participant's eligibility as per protocol criteria and that an appropriate informed consent has been obtained. Ethic's board/IRB approval for the protocol must be on file at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

9. ONLINE DATA CAPTURE SYSTEM

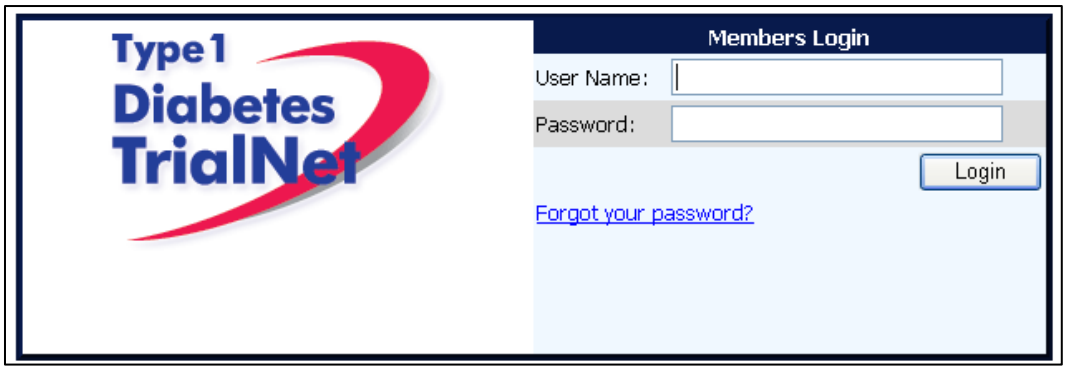
9.1 Overview and Basic Functionality

9.1.1 Login/Navigate to the TN16 Protocol Manager Area

Step 1. Procedure to login and navigate to the TN16 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.

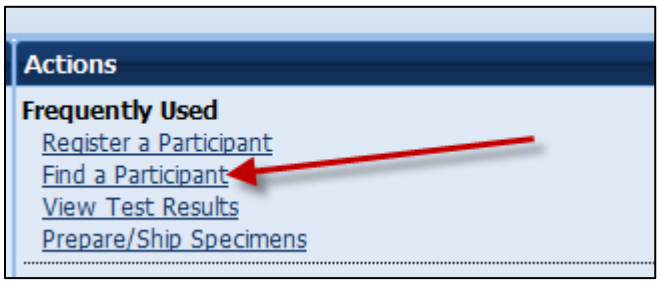


Step 3. Navigate to the “Protocols” portlet. Under TN16, select “Protocol.”

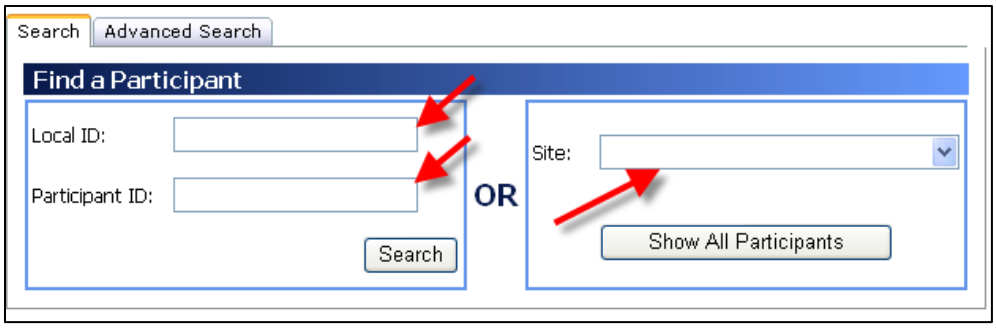
9.1.2 Finding a Participant

This procedure will be done for every visit.

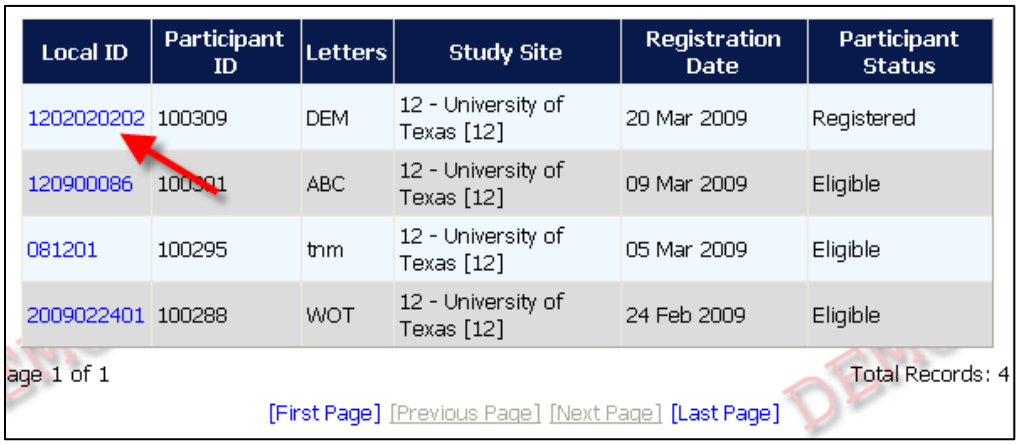
Step 1. Procedure to find participant: Once in TN16 Protocol, navigate to the "Actions" portlet and select "Find Participant."



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



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.

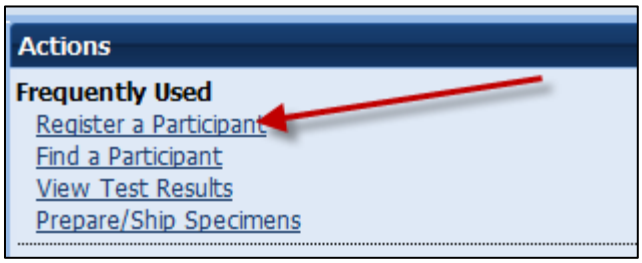


Local ID	Participant ID	Letters	Study Site	Registration Date	Participant Status
1202020202	100309	DEM	12 - University of Texas [12]	20 Mar 2009	Registered
120900086	100301	ABC	12 - University of Texas [12]	09 Mar 2009	Eligible
081201	100295	tnm	12 - University of Texas [12]	05 Mar 2009	Eligible
2009022401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

9.1.3 Registering a Participant

Step 1. Log into TrialNet Members Website and navigate to the Protocols portlet. Select the "Protocol" link under TN16 –Long Term Follow Up.

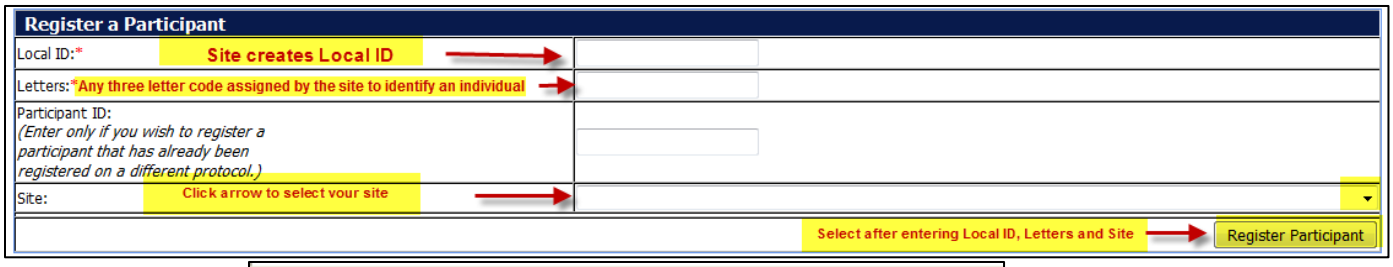
Step 2. Once in TN16 Home Page, navigate to the Actions portlet and select "Register Participant."



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

a. Local ID: The site can enter the desired local ID for the participant or can enter the same local ID as used from originating study. This can include numbers and letters.
b. Letters: Enter the three letter code as used on the protocol the participant is originating from.
c. Participant ID: Enter the participant **ID that was used on the protocol the participant is originating from.**
d. Site: Select applicable site.

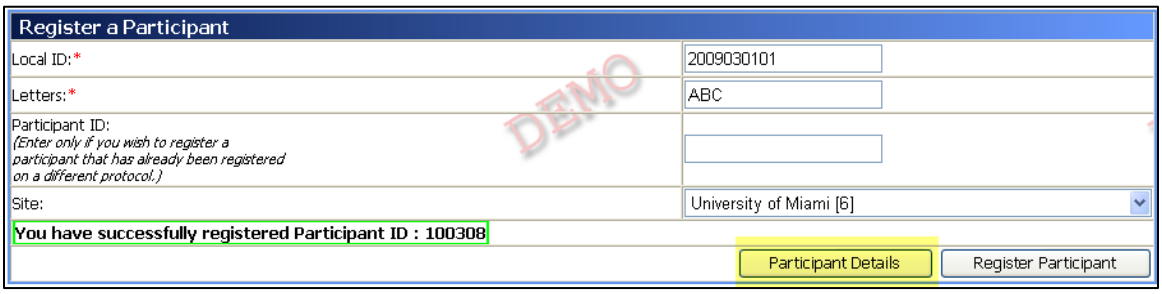
Step 4. Click on the Register Participant. A success message with the auto-generated Participant ID will appear. For example :



You have successfully registered Participant ID : 100308

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

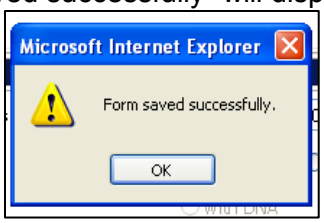
Step 6. If you want to view the participant details for the newly registered subject, select the “Participant Details” button at the bottom of the “Register a Participant” box.



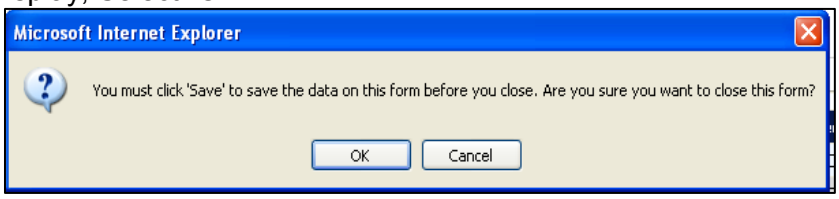
9.1.4 Save and Close e-CRFs

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

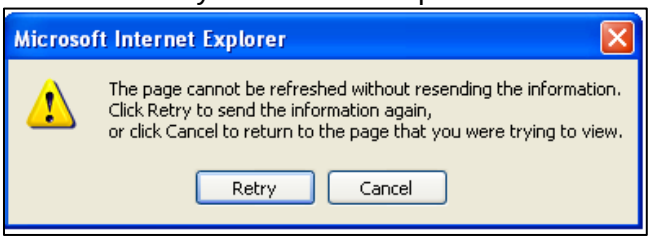
Step 1. Procedure to save and close-out form: After entering the data select “Save”. The message “Forms saved successfully” will display.



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.”



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.

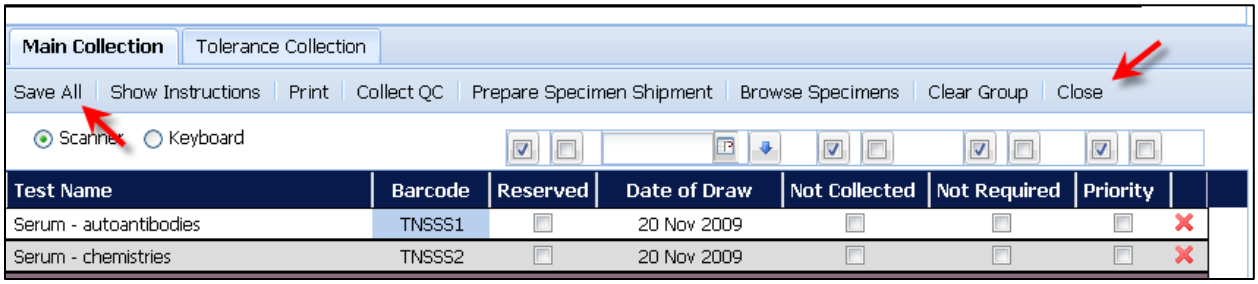


9.1.5 Save and Close Specimen Collection Forms

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.

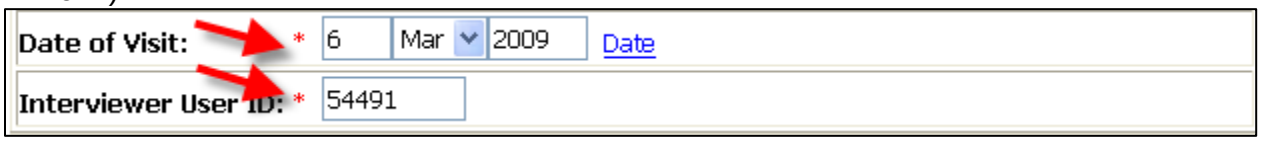


Please review the TrialNet Specimen Management System User Manual for potential error messages you may receive when attempting to save a collection form and additional information regarding collection forms.

9.1.6 Form Required Fields

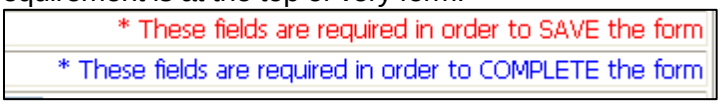
There are two kinds of required fields on every form:

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



2. 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 very form:

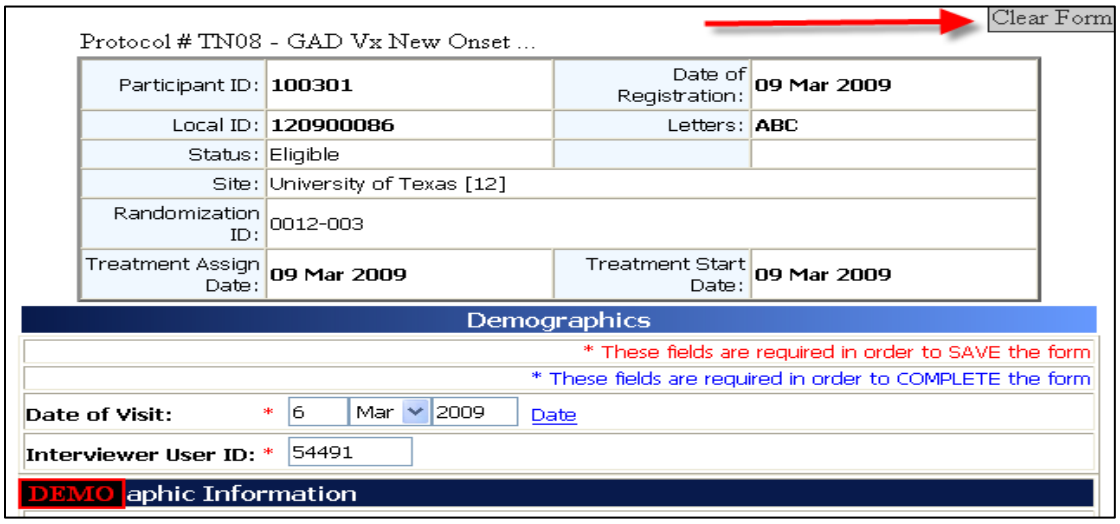


9.1.7 Clear ALL Data from a Form

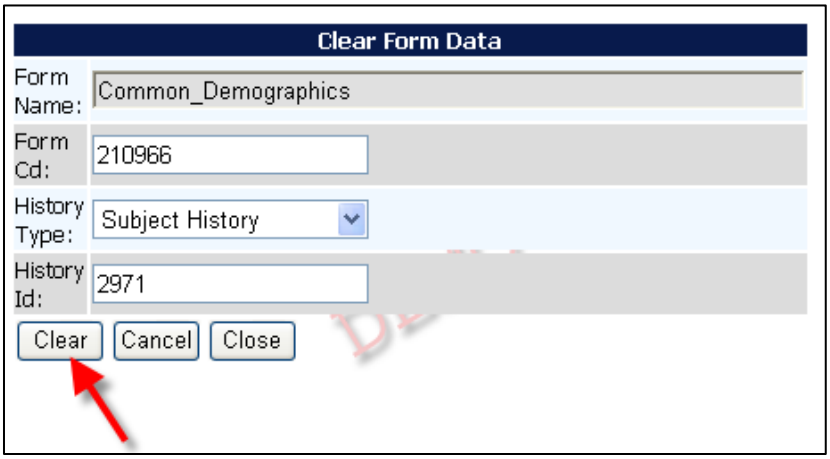
If you find you have mistakenly entered wrong data on a form, you can clear all data on the form as long as you are the person who entered the data on the form (determined based on the Interviewer user ID entered in the form).

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

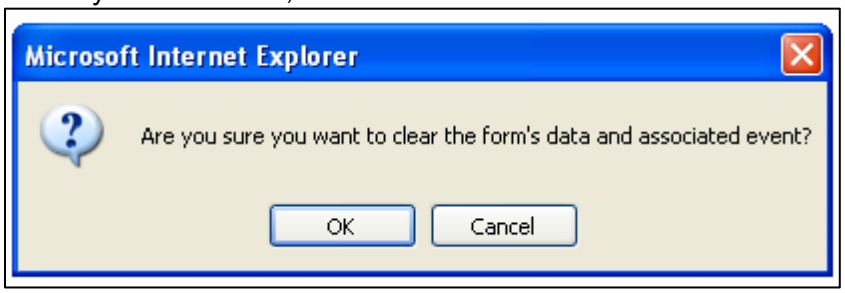
Step 2. Click on the button entitled “Clear Form” in the upper right hand corner of the screen.



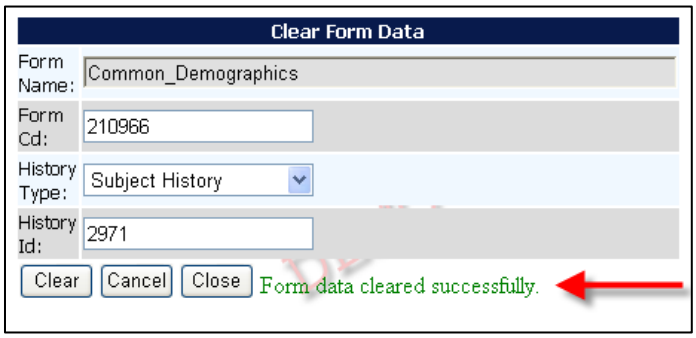
Step 3. The page will navigate to a description of the form you are about the clear (Clear Form Data box). If you are certain you wish to clear out all data on the form, click the button “Clear.”



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.

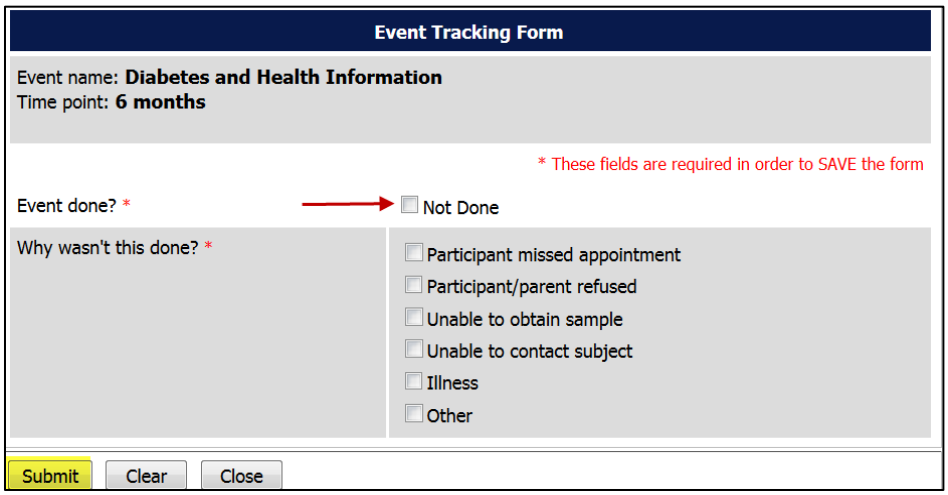
9.1.8 Clear ALL Data from a Collection Form

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
Baseline	Registration Form	
	Eligibility	Tracking
	Diabetes and Health Information	Tracking
	Baseline Specimen Collection	Tracking

- Time Point – When this event occurs in the timeline that starts at registration (e.g. Screening, Initial Visit , Visit 1, etc)
- Event Title – Title of the Event/Form (e.g. Eligibility, Diabetes and Health Information , etc.
- Tracking – The Event Tracking Form. This form should be completed if the Diabetes and Health information eCRF was not completed during a visit and/or if no specimen(s) were collected at all.



- 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.

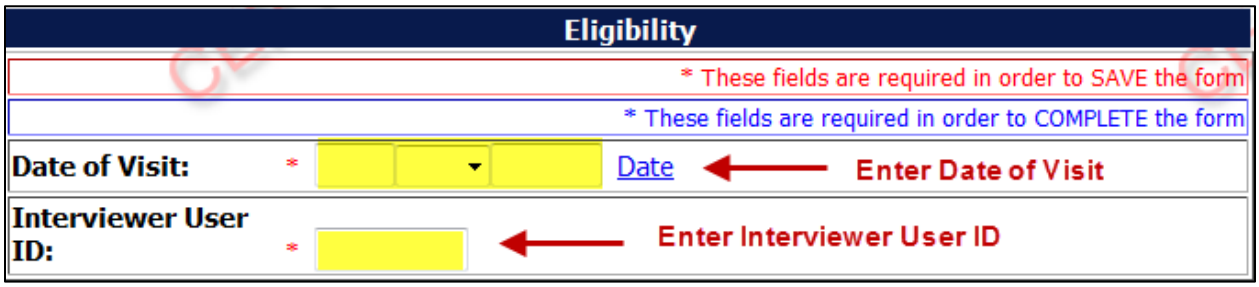
9.3 Visit Forms

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.

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



Step 4. Complete all sections of the form

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)

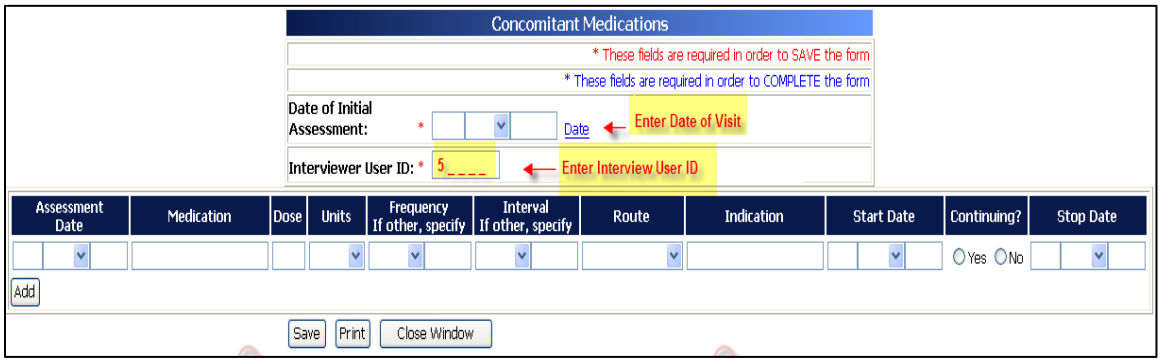
9.3.2 Concomitant Medications

Step 1. Select the form from the participant details screen, and enter Date of Visit and your Interview User ID.

Step 2. Complete all sections for each medication listed. Do not complete this form if the participant reports they are not taking any medications.

Step 3. This form should up updated at every visit with any additional medications the participant takes including any prescription and over the counter medications.

Note: The con meds form is a continuous running log. The form will be denoted as "complete" under Event Status for all visits after the first entry is made. All data entered will be displayed at all visits.



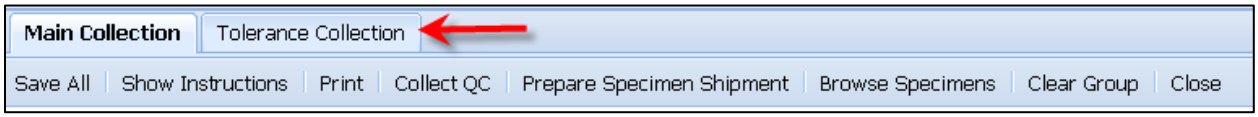
9.3.3 Specimen Collection Form: Main Collections

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 for the TN16 LIFT study include OGTTs, and MMTTs.

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

9.3.4 Specimen Collection Form: Tolerance Collections

Tolerance collections for the TN16 LIFT study include OGTTs, 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.



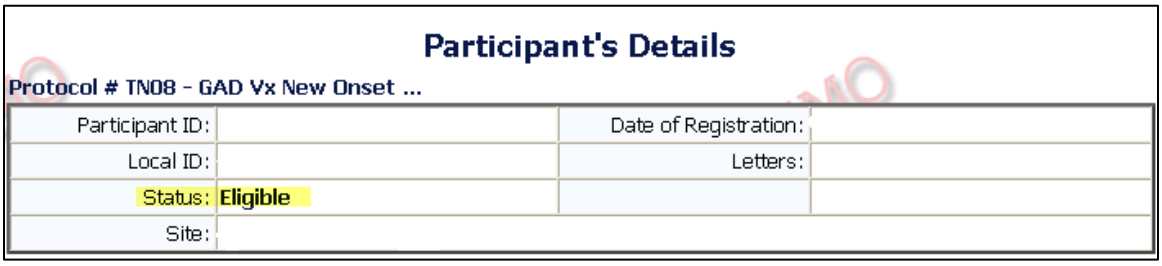
After completing the Main Collections navigate to the "Tolerance Collection" by selecting the "Tolerance Collection" tab.

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

9.3.5 Initial Eligibility Form

This form will determine the status of the participant's eligibility in the study.

After saving the completed form check the Participant Details screen to see if status of participant changed from Registered to Eligible.



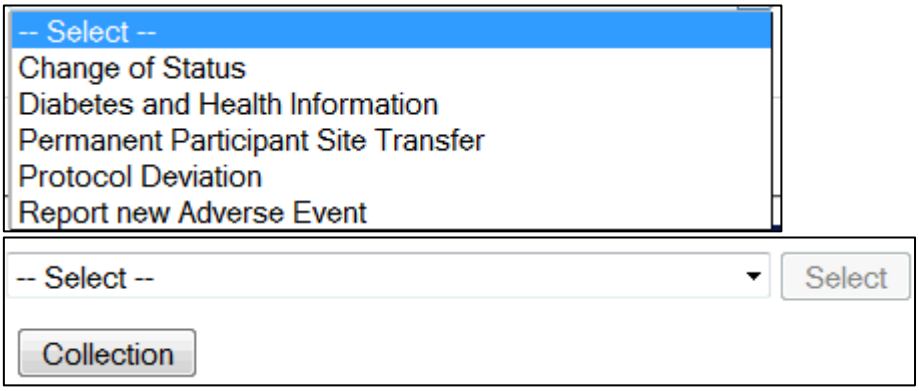
9.4 PRN Forms

The forms available under the Additional Study Forms/Events should be completed as needed:

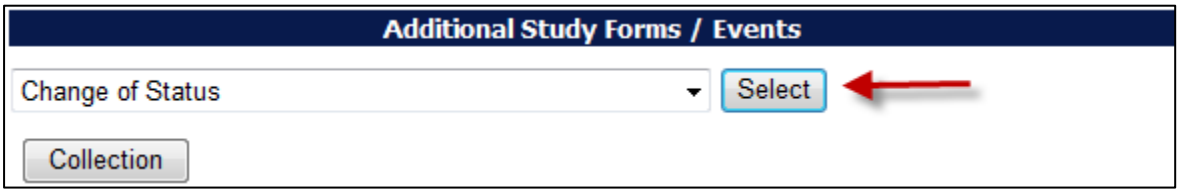
9.4.1 Open a New Additional Study Form/Event (PRN Form)

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.

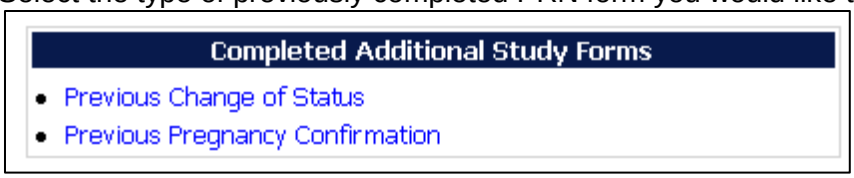


Step 4. A new window will open with the selected form.

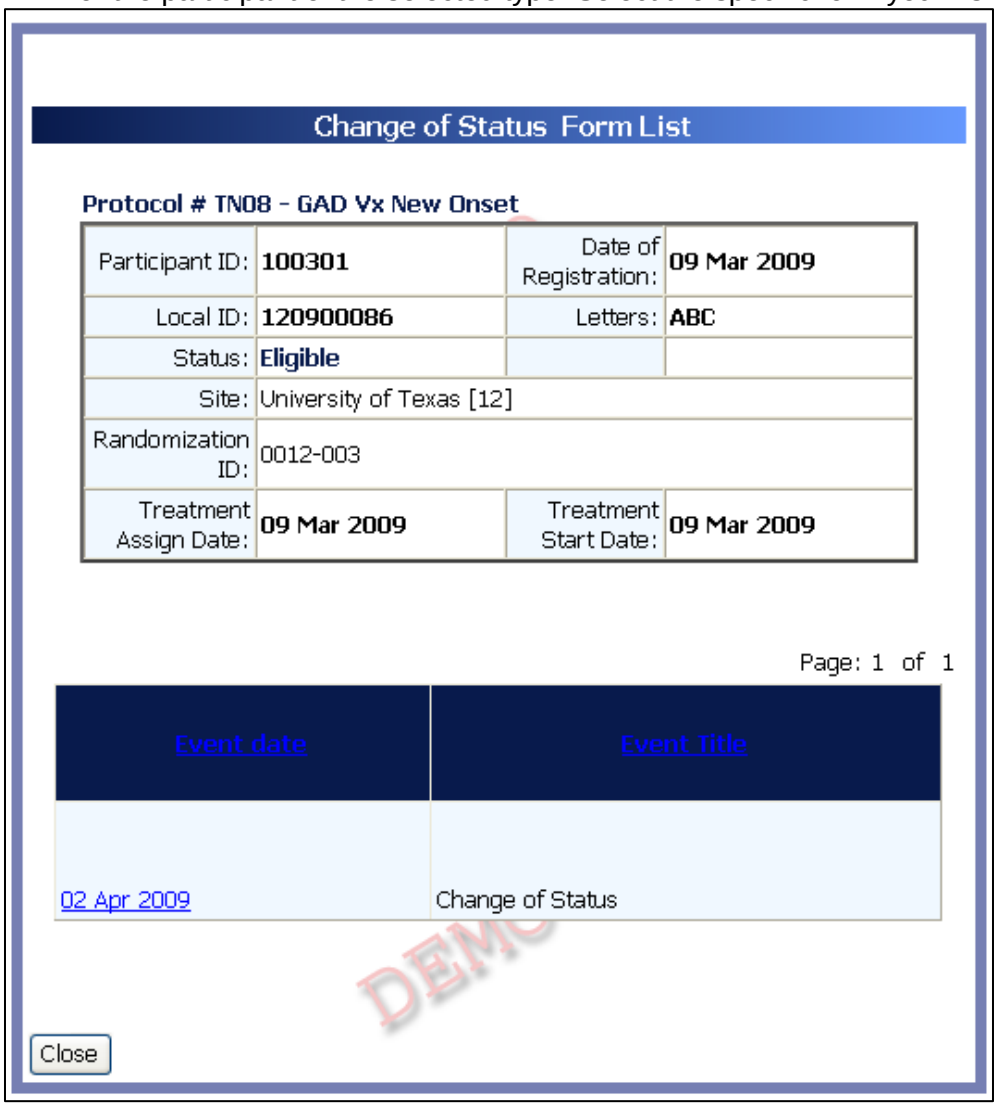
9.4.2 Open a Previously Completed Additional Study Form/Event (PRN Form)

Step 1. 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 2. Select the type of previously completed PRN form you would like to view



Step 3. 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.



Step 4. The previously completed form will open in a new window.

9.4.3 PRN 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 trial an adverse event is: "…any occurrence or worsening of an undesirable or unintended sign, symptom or disease specifically associated with study procedures."

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, **are only related to the TN16 LIFT 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 only with the 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/ctcaev3.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.

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.

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.

a. To save this report, WITHOUT SUBMITTING, select "Save draft."
   i. 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.
b. To submit the report, click on "Submit for review."
   i. Selecting "submit for review" automatically saves the event as well.
c. 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	(DD MMM YYYY) *

B. ADVERSE EVENT REPORT

Adverse event occurrence date	(DD MMM YYYY) *
Is this a primary or secondary event?	○ Primary ○ Secondary* (required only for initial report) If secondary event, enter primary Adverse Event ID:

C. EVENT DESCRIPTION

Event Category	*Help
Event Supra-term "Type of Event"	*
Event Select "Site or Modifier"	* (required only if options are present in drop down list)
Severity	*
Event Details "Description"	
Location of event treatment	Other

D. EVENT ASSESSMENT

Expected	○ Yes ○ No *
Causality (by reporter)	*
Was the adverse event associated with any of the following? (check all that apply)	☐ Development of a congenital anomaly or birth defect ☐ Development of a permanent, serious, disabling or incapacitating condition ☐ Death ☐ Hospitalization or prolonged hospitalization ☐ Life threatening ☐ Is another condition which investigators judge to represent significant hazards
Patient status (at time of report):	*
Adverse event resolved date	(DD MMM YYYY)
Date of death	(DD MMM YYYY)
Additional comments	

E. Study Drug Activity

Study Drug Start Date (DD MMM YYYY)	Study Drug Stop Date (DD MMM YYYY)

Add

Did the event/reaction abate after stopping drug?	○ Yes ○ No ○ Not Applicable
Did the event/reaction reappear after reintroduction?	○ Yes ○ No ○ 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	

Save Form | Submit for Review | Print | Close Window

Details of Initial and Previous Follow-up Reports:

DEMO

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. *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.

*Date **cannot** be prior to patient registration date.*

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?	Primary Secondary* (required only for initial report) If secondary event, enter primary Adverse Event ID:

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	*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"	*

- *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"	* (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. *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.

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	Yes No *

- *Causality (by reporter)*:This refers to the relatedness of the event to the investigational product. 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. *AE seriousness does not relate to AE Severity.*

Was the adverse event associated with any of the following? (check all that apply)	☐ Development of a congenital anomaly or birth defect ☐ Development of a permanent, serious, disabling or incapacitating condition ☐ Death ☐ Hospitalization or prolonged hospitalization ☐ Life threatening ☐ 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):	*

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

Adverse event resolved date	(DD MMM YYYY)

- *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	(DD MMM YYYY)

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

Additional comments	Provide additional information if not captured elsewhere on the form

Section E. Concomitant Medication:

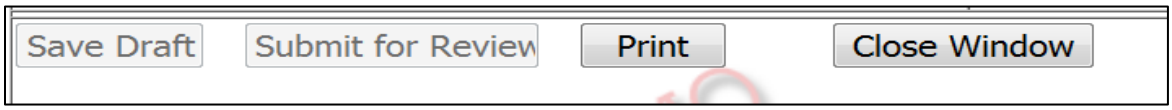
Prior to submitting the adverse event make sure any additional concomitant medications are listed in the concomitant medication running log prior.

F. CONCOMITANT MEDICATIONS
* If applicable, please ensure the concomitant medications log was updated prior to adverse event submission.

Reporter Information:
Reporter User ID: User ID must be completed by person reporting the AE.

REPORTER INFORMATION	
Reporter User ID	

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

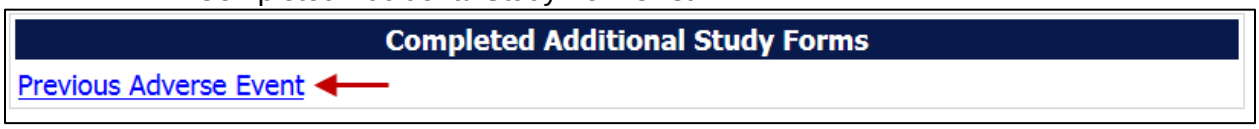


Please Contact aTNCC CRA if there are any additional questions regarding this form.

10.4 Directions for Reporting Follow Up AE's / System Description

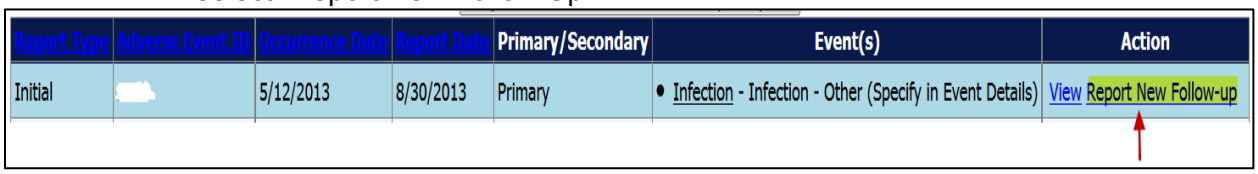
10.4.1 Navigating to the Follow-Up Reporting Form

Step 1. On the Participant's Details page select "Previous Adverse Event" from the Completed Additional Study Forms list:



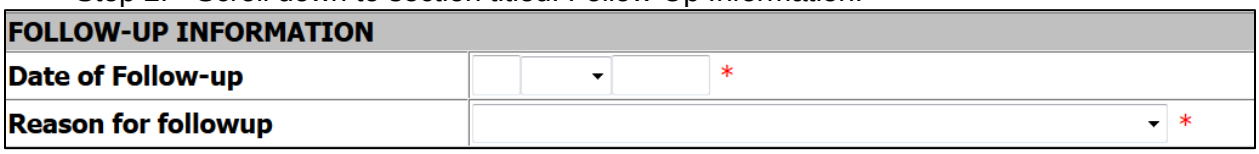
10.4.2 Reporting an Adverse Event

Step 1. Select the Adverse Event that will require a follow up. Under the "Action" column select "Report New Follow Up".



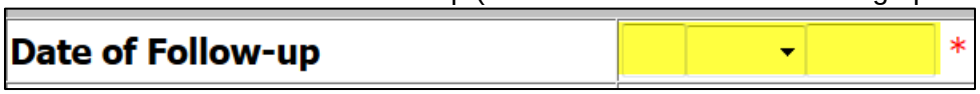
Report Type	Adverse Event ID	Occurrence Date	Report Date	Primary/Secondary	Event(s)	Action
Initial		5/12/2013	8/30/2013	Primary	• Infection - Infection - Other (Specify in Event Details)	View Report New Follow-up

Step 2. Scroll down to section titled: Follow-Up Information.

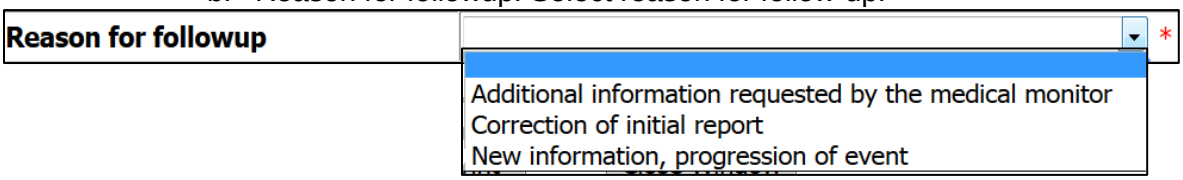


FOLLOW-UP INFORMATION	
Date of Follow-up	*
Reason for followup	*

a. Enter Date of Follow-Up (date = current date AE is being updated).



b. Reason for followup: Select reason for follow-up.

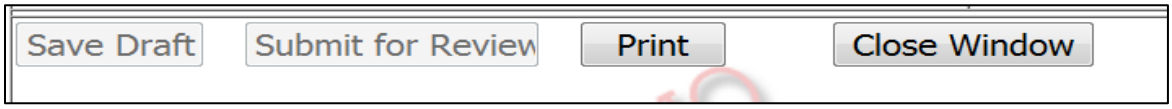


Step 3. Scroll up to either "Additional Comments" or "Event Details Description" and describe reason for follow up. When entering reason, it is recommended to provide current date of follow up.

Example of Follow Up Reason(s):

Additional comments	MM/DD/YY: Modifed Patient status to Recovered/resolved without Sequelae or MM/DD/YY Event was reported in error since the severity is a 1-Mild. Per protocol events reported in system if Grade 2 or higher.

Step 4. Form Dispositon: The AE can either be: Save a draft; or submit for review, print, or simply close a window.



Please contact a TNCC CRA if there are any additional questions regarding this form.

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 TN16-Long Term Follow Up homepage, there are a series of portlets meant to assist/aid sites in the conduct of the study.

11.1 TN16 – Working Documents Portlet

From the TN16-Long Term Follow Up 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.

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. Initial Submission Checklist
    b. Visit Checklists
2. Forms
    a. Lab Forms
    b. eCRFs
3. Assessment Tools
    a. Template source documents
4. Reimbursement Schedule

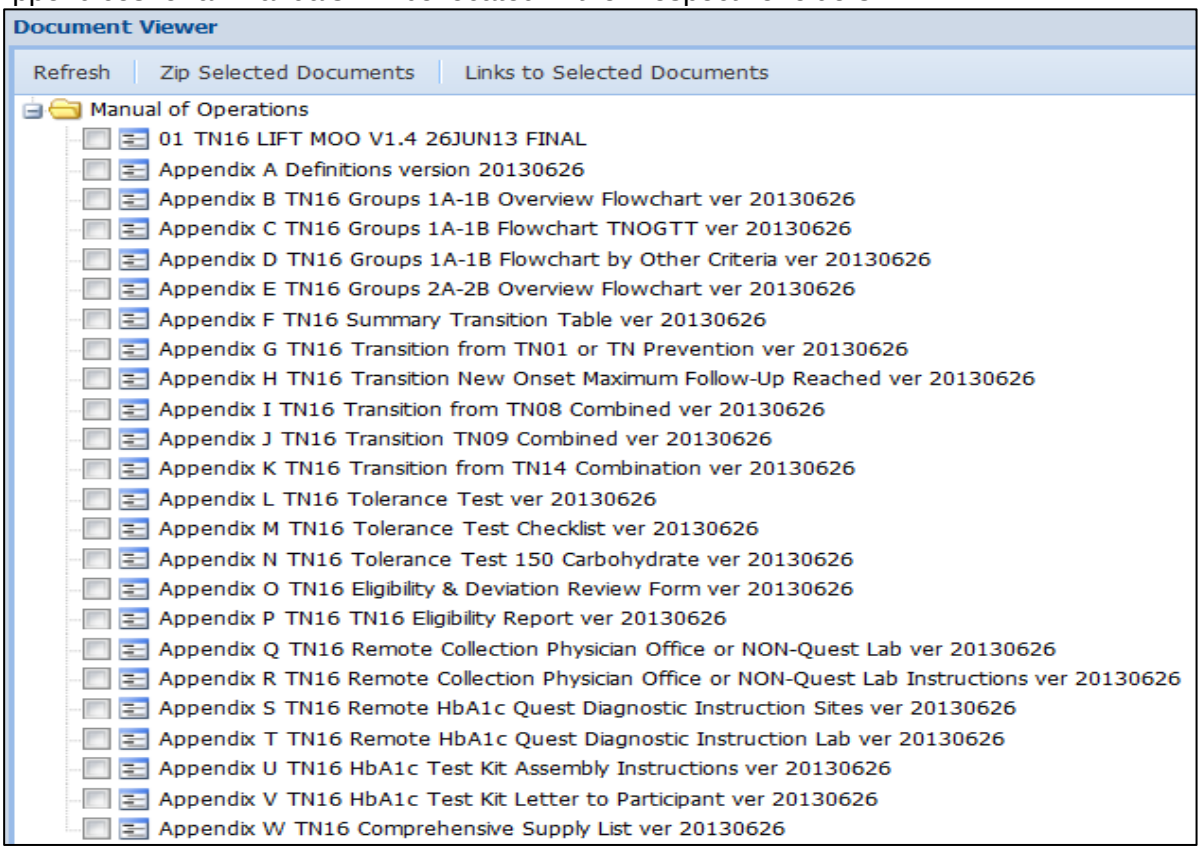
5. Training Documents
    a. Training Presentations and materials related to the study

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)
    a. Tracked and clean versions of the current MOO
    b. Protocol specific appendices
    c.
2. Lab Manual
    a. Current Lab MOO
    b. Protocol specific appendices

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



11.1.4 Archive

Under the "Archive" header are previous versions of all study-related documents for the site's reference.

11.2 TN16 – Actions Portlet

From the TN16-Long Term Follow Up homepage, all study-related actions are available in the "Actions" portlet.

11.2.1 TN16- 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.

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

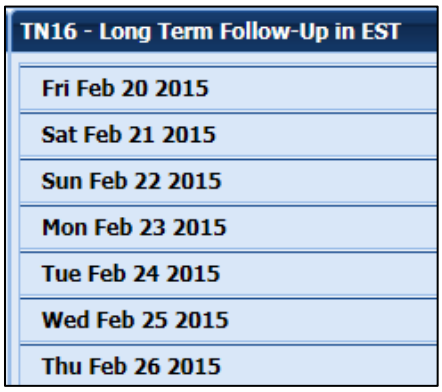
Under the “Supplies” actions header is a link to the Supply Ordering System (SOS).

11.3 TN16 – Contacts

From the TN16-Long Term Follow Up homepage, all study-related contacts are available in the “Contacts” portlet.

11.4 TN16 – Calendar

From the TN16-Long Term Follow Up homepage, all study-related calls, trainings and event are noted in the “Calendar” portlet.



11.5 TN16 – Protocol Development Committees

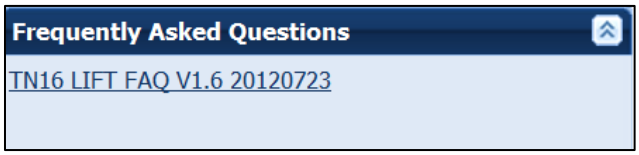
From the TN16-Long Term Follow Up homepage, links to the Protocol Chair Committee and Study Group Committee pages are located under the “Protocol Development Committee” portlet.

11.6 TN16 – Publications

From the TN16-Long Term Follow Up homepage, all protocol specific publications, ancillary publications and data sharing policies are located under the “Publications” portlet.

11.7 TN16 – Frequently Asked Questions

From the TN16-Long Term Follow Up 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 1. 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.

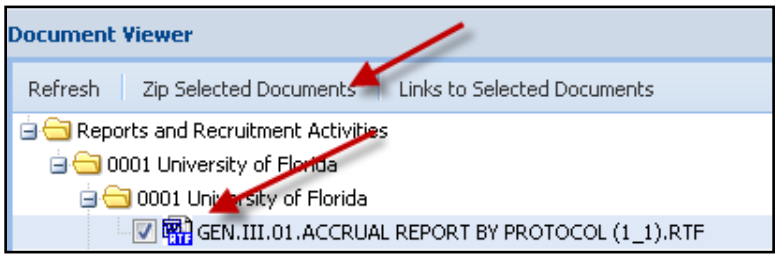
Step 4. Once you open the "General Reports" folder, you will be able to access general accrual reports for all TrialNet protocols for your clinical center and affiliate sites.

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 TN16-Long Term Follow Up 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 TN16 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	TN16.I.01.Accrual Report By Clinical Center.rtf	Accrual totals, by clinical center	Monthly
	TN16.I.02.Actual.v.Expected Accrual - Graph.rtf	Graph of actual verses expected accrual.	Monthly
	TN16.I.03.IRB Summary - Ethnicity, Race and Gender Report.rtf	IRB summary of ethnicity, race and gender for all subjects	Monthly
	TN16.I.04.Adverse Event Summary Report.rtf	Summary of all reported AEs and SAEs	Weekly
Site Reports ↓ General Reports	TN16.II.01.Accrual Report By Institution (CC#).rtf	Accrual summary for clinical center and all affiliates	Monthly
	TN16.II.01.LIFT-Summary of Eligible Participants from Prevention Studies (CC#).rtf	Potentially eligible participants for TN16 by site	Daily
	TN16.II.02.IRB Summary - Ethnicity, Race and Gender Report (CC#).rtf	IRB summary of ethnicity, race and gender for each site	Monthly
	TN16.II.03.Summary of Screening BAA from Prevention Studies (CC#).rtf	Summary of Screening BAA results from Pathway to Prevention and Prevention Studies	Daily
Site Reports ↓ Site Folder	TN16.III.01.Accrual Report (CC#_Site#).rtf	Displays protocol accrual totals	Monthly
	TN16.III.02.IRB Summary - Ethnicity, Race and Gender Report (CC#_Site#).rtf	Displays IRB summary of ethnicity, race and gender	Monthly

	TN16.III.03.Adverse Event Summary Report (CC#_Site#).rtf	Displays summary of all AEs and SAEs	Monthly
	TN16.III.09.Particpant Schedule of Visits Report (CC#_Site #).rtf	Displays a calendar of target dates for subjects' visits	Daily
	TN16.III.11.LIFT-Eligible Participants (CC#_Site #).rtf	Displays potentially eligible participants for TN16	Daily

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** –scheduling wheels, recruitment and retention materials, diabetes management supplies.

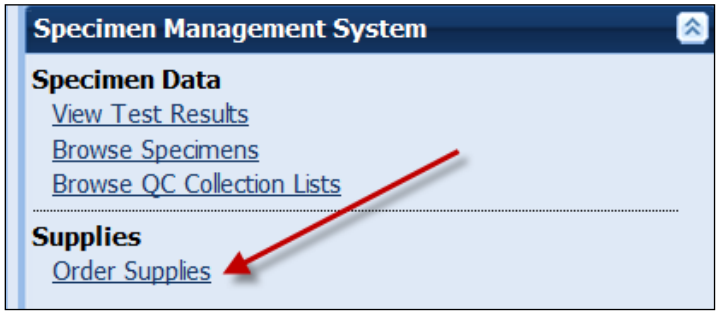
The TNCC reviews and approves all orders placed in the Fisher online system within 48 hours and contacts TradeWinds to fulfill etched vial orders. Some supplies are directly supplied by the USF TNCC, including lifestyle questionnaires, scheduling wheels, teleforms, and recruitment materials.

13.2 Ordering Supplies

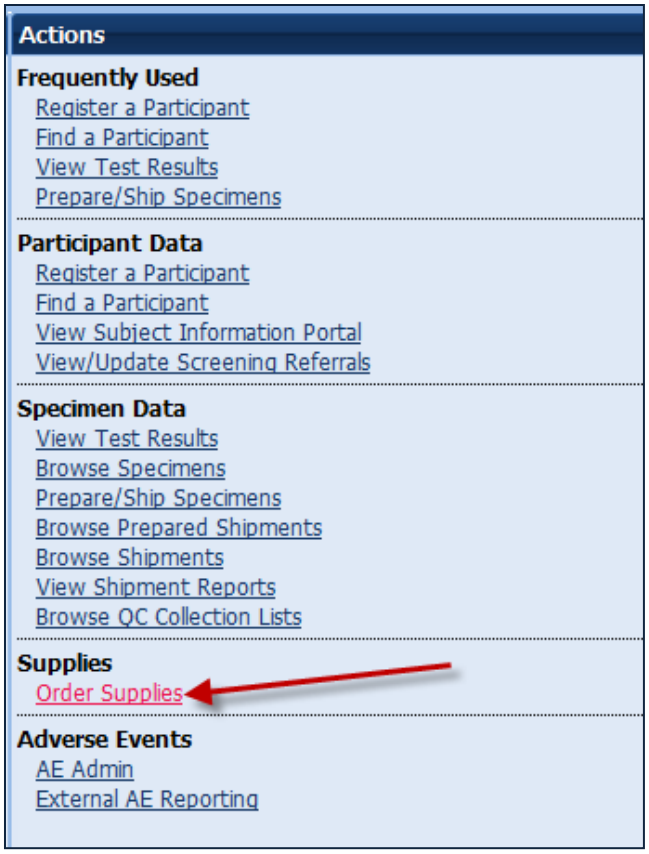
13.2.1 Navigating the Fisher BioServices Supply Ordering System (SOS)

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

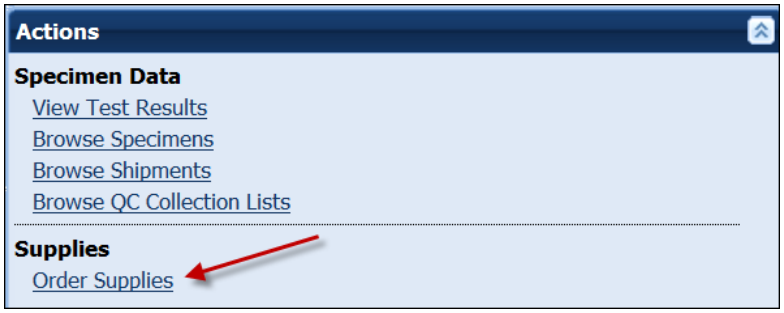
From the members website main page, navigate to the "Specimen Management System" portlet on the left hand side of the page and select "Order Supplies."



From the TN16 Long Term Follow Up Study homepage, navigate to the central "Actions" portlet and select "Order Supplies."



From the Specimen Processing References Page, navigate to the "Actions" portlet and select "Order Supplies".

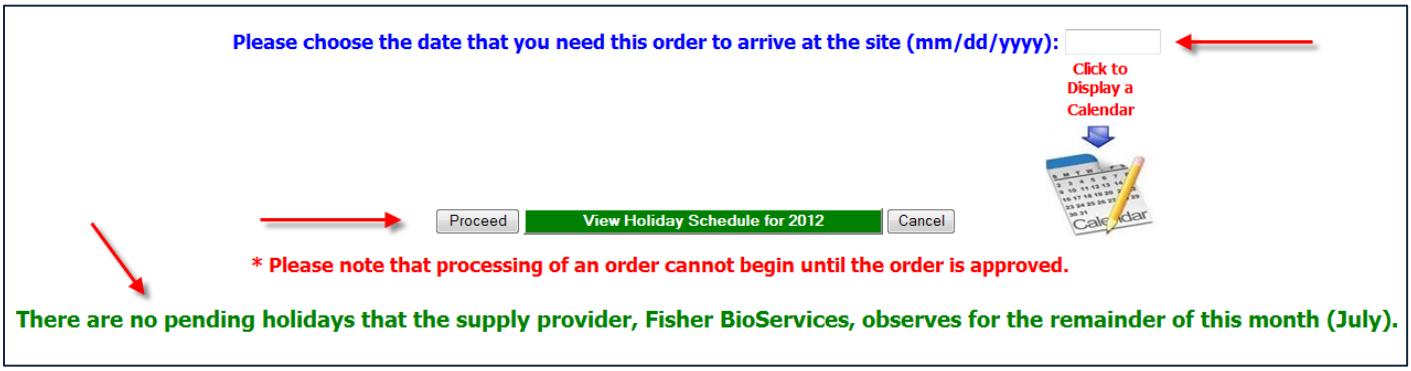


Step 2. The Supply Ordering System (SOS) web page will appear in a new window. You will be prompted to enter your TrialNet Supply Order System Login information.

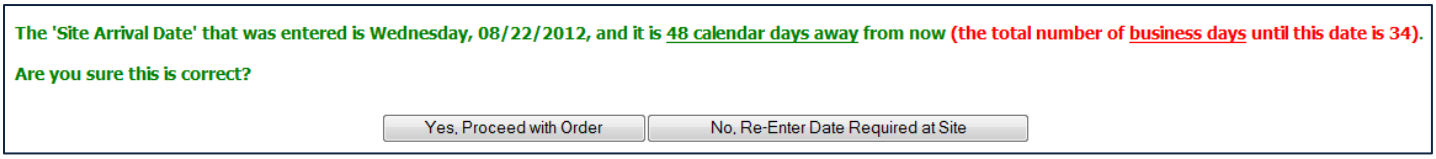
If you do not have a login, please contact the TNCC to obtain a user account.

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



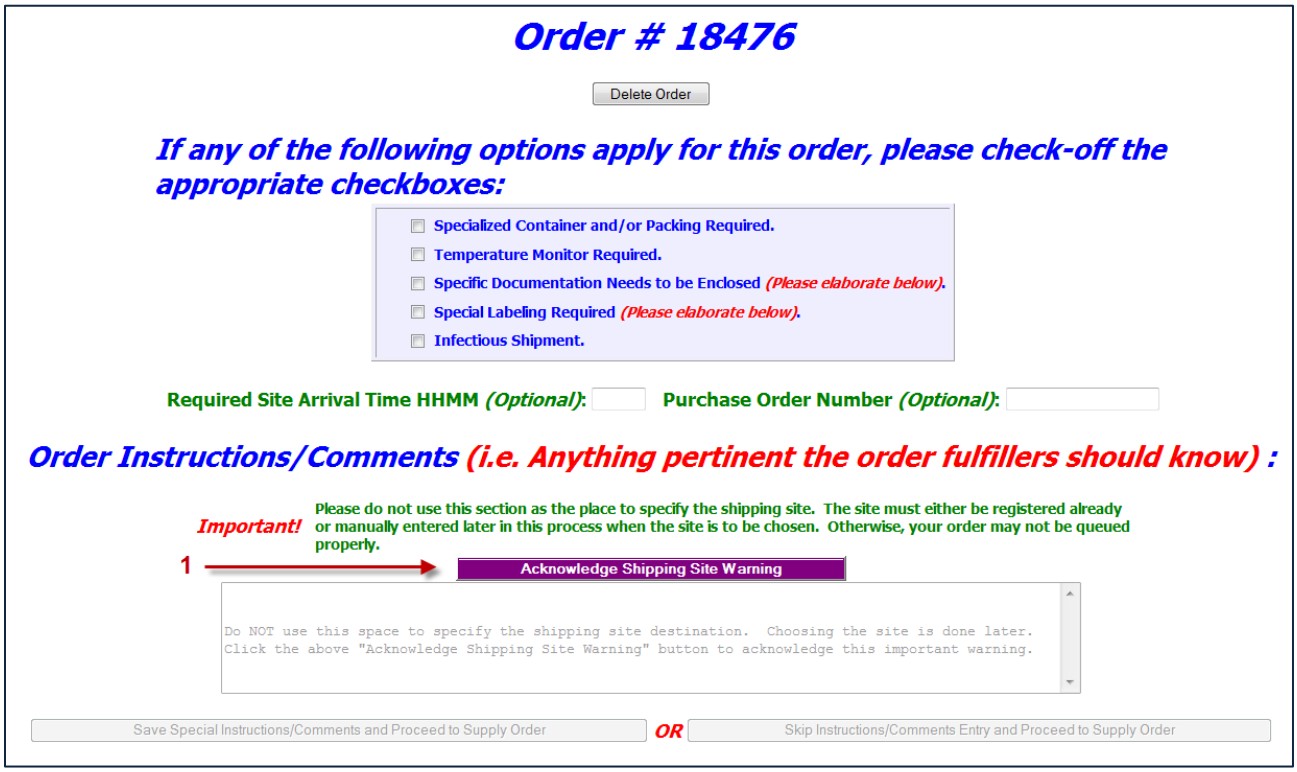
Step 5. After entering the date and selecting "Proceed" you will be prompted to confirm the date and either select proceed or opt to re-enter the date. If the date you have selected is OK, please select "Yes, Proceed with Order." If not then select "No, Re-Enter Date Required at Site."

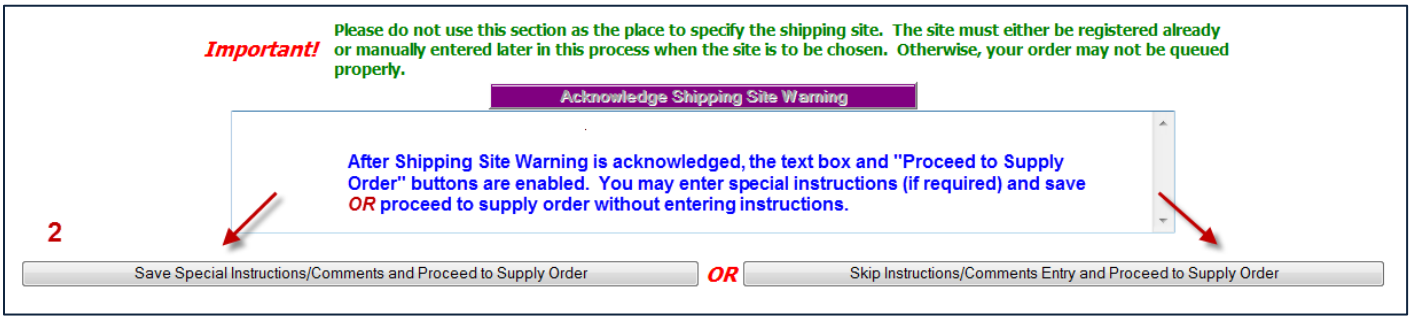


Step 6. Once you have confirmed the date is correct and selected "Yes, Proceed with Order" you will be prompted to enter order instructions or comments OR proceed to the order without special instructions:

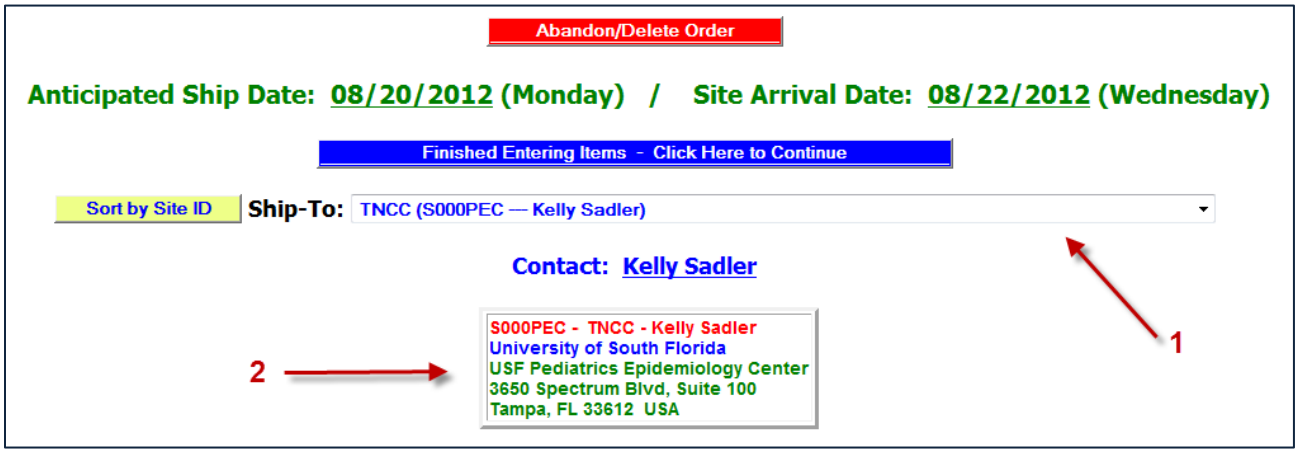
a. If you would like to enter special instructions, please enter them into the box provided and select "Save Special Instructions/Comments and Proceed to Supply Order."

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.”

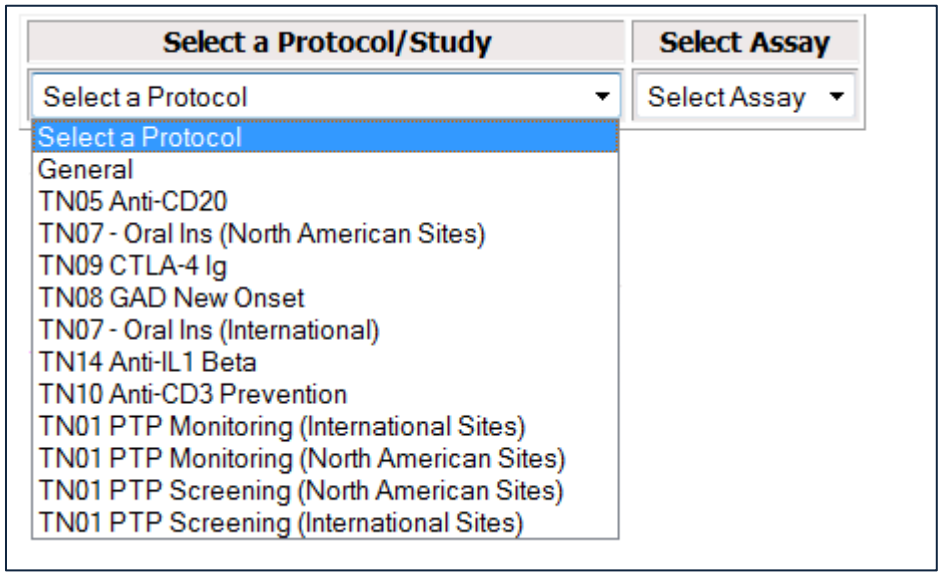




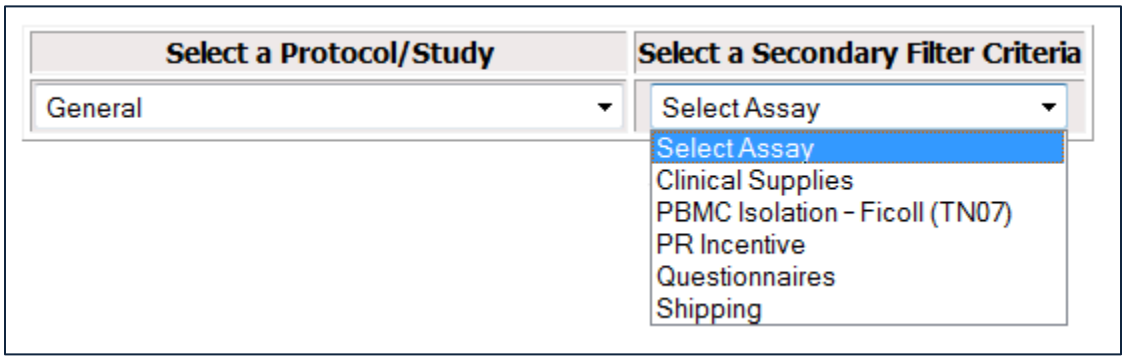
Step 7. Enter the “Ship to Site” by selecting a site from the “Ship-To” dropdown menu.



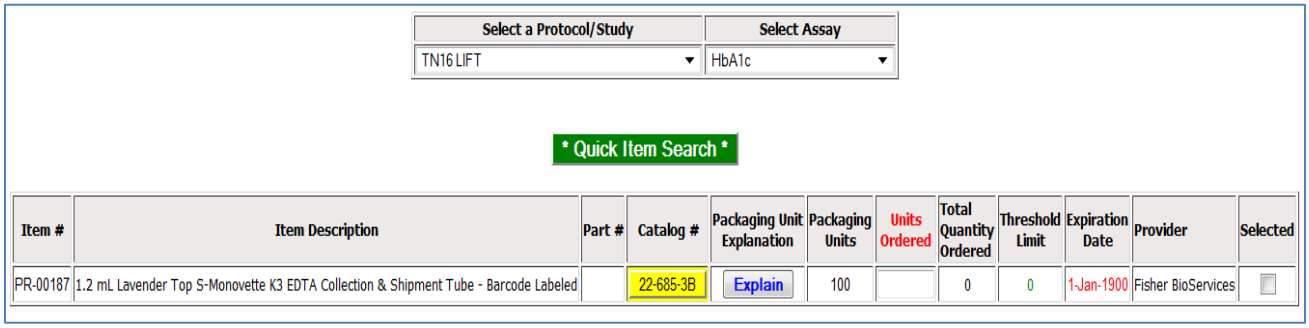
Step 8. Select the Protocol/Study and Assay for which you want to order supplies.



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.



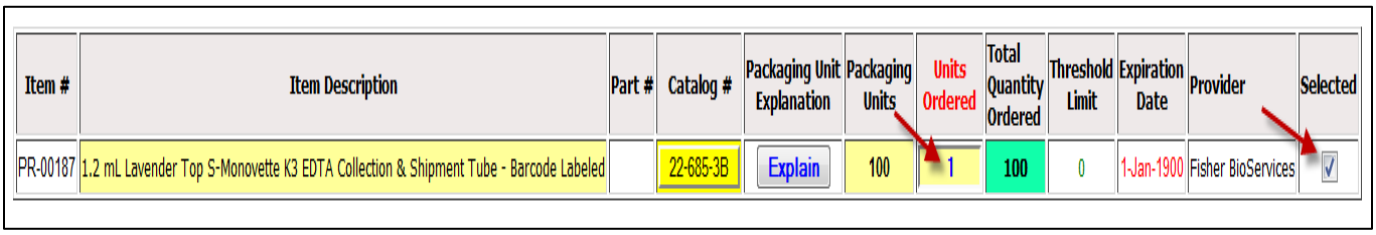
Step 9. Once a Protocol and Assay are selected, the window will refresh and the applicable supplies will populate below.



Item #	Item Description	Part #	Catalog #	Packaging Unit Explanation	Packaging Units	Units Ordered	Total Quantity Ordered	Threshold Limit	Expiration Date	Provider	Selected
PR-00187	1.2 mL Lavender Top S-Monovette K3 EDTA Collection & Shipment Tube - Barcode Labeled		22-685-3B	Explain	100		0	0	1-Jan-1900	Fisher BioServices	

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.

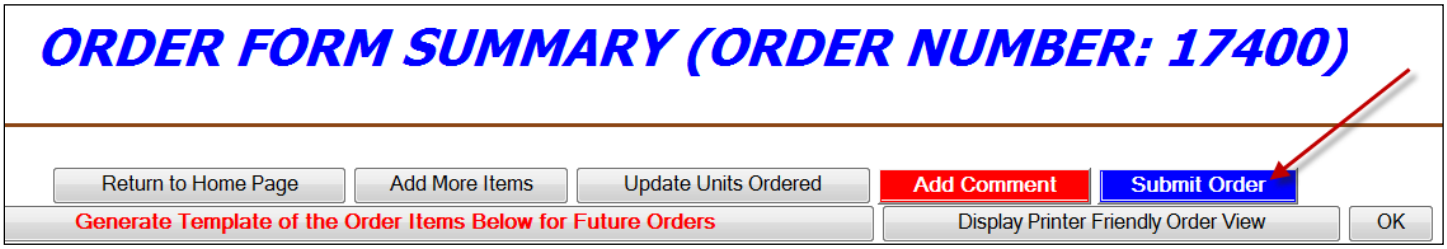
For example, 1 unit of the 1.2 mL Lavender Top S-Monovette K3 EDTA collection and shipment tubes contains 100 tubes. Since 1 units were ordered below, a total of 100 tubes will be shipped.



Item #	Item Description	Part #	Catalog #	Packaging Unit Explanation	Packaging Units	Units Ordered	Total Quantity Ordered	Threshold Limit	Expiration Date	Provider	Selected
PR-00187	1.2 mL Lavender Top S-Monovette K3 EDTA Collection & Shipment Tube - Barcode Labeled		22-685-3B	Explain	100	1	100	0	1-Jan-1900	Fisher BioServices	✓

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.



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).

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.

More information about each item offered is available by clicking on one of the links.

- For all items provided by Fisher BioServices, the "Click to view Product Description" button will open a new window, directing you to the Manufacturer website or catalog listing.
- For all items excluding PBMC Freeze Media Kits, the "Click to view supply" button will open a new window with a close-up picture of the exact item you will receive if you placed an order.

Item #	IN-TRAK Product ID	Shipping Temp	Protocol	Assay	Item Description	Packaging Units	ID Specific	Kit	Catalog #	Supply Picture	Provider	Threshold Limit	Expiration Date
PR-00001	PR-00001	Ambient	General	Clinical Supplies	Absorbent Pads	250	No	No	Click to viewProduct Description	Click to view supply	Fisher BioServices	0	
PR-00001	PR-00001	Ambient	General	Shipping	Absorbent Pads	250	No	No	Click to viewProduct Description	Click to view supply	Fisher BioServices	0	
PR-00002	PR-00002	Ambient	General	Clinical Supplies	Alcohol Swabs	100	No	No	Click to viewProduct Description	Click to view supply	Fisher BioServices	0	
PR-00003	PR-00003	Ambient	General	Clinical Supplies	Angiocatheter, 20 G (Insyte)	50	No	No	Click to viewProduct Description	Click to view supply	Fisher BioServices	0	31-Oct-2016

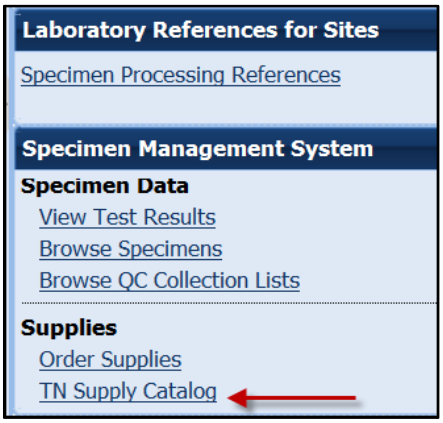
The table below lists all filter criteria applicable to the TN16 Long Term Investigative Follow-Up Study.

TN16 Long term Investigative Follow-Up Supply Organization	
"Protocol" Filter Criteria	**"Test/Assay" Secondary Filter Criteria**
TN16 LIFT (North American Sites)	Handbooks HbA1c MMTT- 2Hour OGTT Whole Blood – PBMC/Plasma Whole Blood – RNA

	Mechanistic Serum Remote Collection -HbA1c
TN16 LIFT (International Sites)*	Handbooks HbA1c OGTT MMTT – 2Hour Whole Blood – RNA Mechanistic Serum
General Supplies	Clinical Shipping PR Incentive

**International sites will NOT collect PBMC/Plasma until further notice.*

For a complete list of all items available for order, please refer to the TN Supply Catalog which organizes supplies by Item # and includes a description and image for each. The catalog is available on the TrialNet members' website homepage in the Supplies section of the Specimen Management System portal.



14. APPENDICES

Appendix A Definitions TN16 MOO ver. 12FEB2015
Appendix B Initial Visit Eligibility Report MOO Ver. 13MAR2015
Appendix C Group 1 Overview Flowchart 20150313
Appendix D Group 2 Overview Flowchart 20150212
Appendix E Summary Transition Table 20150212
Appendix F Transition from TN01 or TN Prevention 20150212
Appendix H Tolerance Test MOO Ver. 12FEB2015
Appendix G Transition New Onset Maximum Follow-Up Reached 20150212
Appendix I Tolerance Test Checklist MOO Ver. 12FEB2015
Appendix J Tolerance Test 150 Carbohydrate 20150212
Appendix K Comprehensive Supply List 20150212
Appendix L Remote Collection Physician Office or NON-Quest Lab Site Instructions 20150215
Appendix M Remote Collection Physician Office or NON-Quest Lab Instructions 20150212
Appendix N Remote HbA1c Quest Diagnostic Instruction Sites 20150212
Appendix O Remote HbA1c Quest Diagnostic Instruction Lab 20150212

Appendix P HbA1c Test Kit Letter to Participant 20150212
Appendix Q HbA1c Test Kit Assembly Instructions 20150212