Protocol TN10

Anti-CD3 (Teplizumab) for Prevention of Diabetes in Relatives at-risk for Type 1 Diabetes Mellitus

Dr. Kevan Herold

Manual of Operations
Version 3.0 13Sep13

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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 (17Sep12)

Title	Teplizumab for Prevention of Diabetes in Relatives at Risk for Type 1 Diabetes Mellitus
IND Sponsor	MacroGenics, Inc. Under IND102,629
Conducted By	Type 1 Diabetes Trial Network (TrialNet)
Protocol Chair	Dr. Kevan Herold, Yale University
Accrual Objective	The study plans to enroll approximately 140 - 170 subjects over 5 years. The study is projected to last between 6 - 7 years, depending upon rate of enrollment and number of subjects who develop diabetes.
Study Design	The study is a 2-arm, multicenter, randomized, placebo controlled masked clinical trial. All subjects will receive close monitoring for development of type 1 diabetes.
Treatment Description	Subjects will receive teplizumab + close monitoring for development of type 1 diabetes or placebo + close monitoring for development of type 1 diabetes.
Objective	To assess the safety, efficacy, and mode of action of teplizumab for prevention of type 1 diabetes
Primary Outcome	The primary objective is to determine whether intervention with teplizumab will prevent or delay the development of T1DM in

	high risk autoantibody positive non-diabetic relatives of patients with T1DM.
Secondary Goals	Secondary outcomes are to include analyses of C-peptide and other measures from the OGTT; safety and tolerability; and mechanistic outcomes.
Major Inclusion Criteria	Autoantibody positive relatives of T1DM proband with abnormal glucose tolerance. Age 8-45 years.

1.3 Study Contacts

TN10 Anti- CD3 Study TrialNet Coordinating Center (TNCC)		
USF TrialNet Coordinating Center (TNCC) University of South Florida Pediatrics Epidemiology Center Tampa, FL 33615	Primary Contact: Darlene Amado	Ph.: (813) 396-9466 Fax: 813-910-1243 Email: darlene.amado@epi.usf.edu
	Secondary Contact: Nichole Keaton	Ph.: (813) 396-9461 Fax: 813-910-1245 Email: nichole.keaton@epi.usf.edu

TN10 Anti- CD3 Study Central Pharmacy		
EMINENT Services Corporation 7495 New Technology Way Frederick, MD 21703-9401	Raghu Yaramolu	Ph.: (240) 629-1972 Ext 107 Fax: (240) 629-3298 Email: ryaramolu@emiserv.com

TN10 Core Laboratory Contact Information
Please refer to the TN10 Anti-CD3 Laboratory Manual for a complete list of TrialNet Core laboratories applicable to the TN10 protocol.

For participating site contact information please refer to TN10 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. The only hard copy document required for activation is the FDA 1572. All other documents required for activation should be sent to the TNCC electronically to regulatory@epi.usf.edu (or by Fax to 813-910-5994).

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

1. Appropriate **IRB/ERB approval** (as below, section 3.2).
2. A current **Site Delegation Log (SDL)** detailing the responsibilities of each staff member as designated by the site PI (as below, section 3.3).
3. **Duality of Interest form(s)** for the PI and the main site coordinator (as below, section 3.4).
4. **Statement of Investigator, Form FDA 1572** (as below, section 3.5).
5. **Screening and Intervention Consent**
6. A completed **New Affiliate Application** consisting of the following forms:
    a. Site Information Form (SIF)
    b. W9/W8 BEN (W8-BEN is used by non-US sites)
    c. New User forms for all site members listed on the Site Delegation Log
    d. Signed and Dated copy of PI's Curriculum Vitae (CV)
    e. TrialNet Confidentiality Agreement completed by all members listed on the SDL
    f. All persons listed on the SDL should complete an IRB/ERB approved human subjects education course

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

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

Requirements for IRB/ERB Approval:

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

3.3 Site Delegation Log

Requirements of the Site Delegation Log:

1. A separate log must be maintained for each protocol

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

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

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

3.4 Duality of Interest Forms

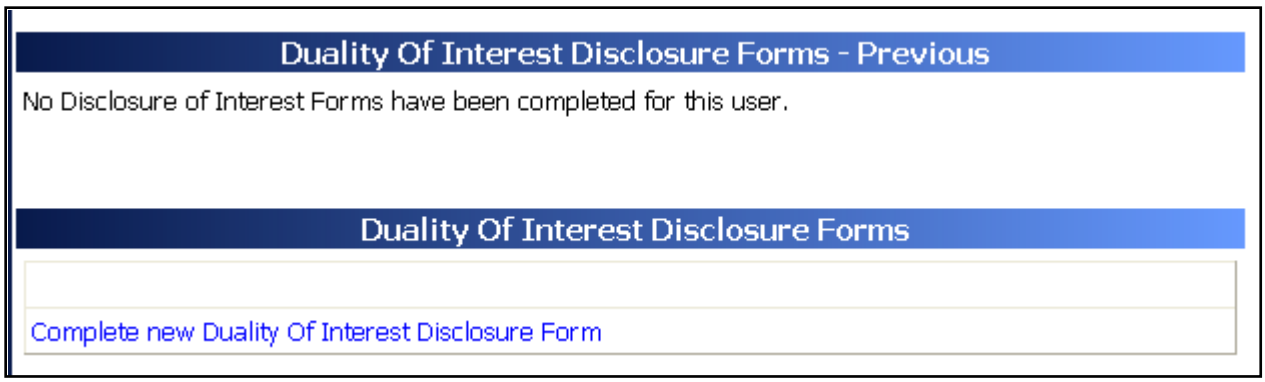
Site activation will require a completed duality of interest form from a minimum of both the PI and main site coordinator.

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

To access the Duality of Interest form:

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

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



Step 3. Read and complete the Duality of Interest Disclosure Form. It is important to pay special attention to section 11 – Dualities or revisions by protocol.

Step 4. Once finished, hit the "save" button. Red text will display beneath the save button indicating that the form has been saved successfully.

Step 5. Click on the "Close Window" button.

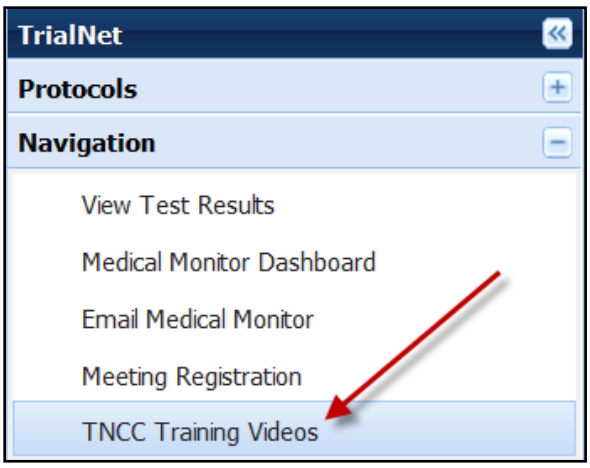
3.5 Study/System Training

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

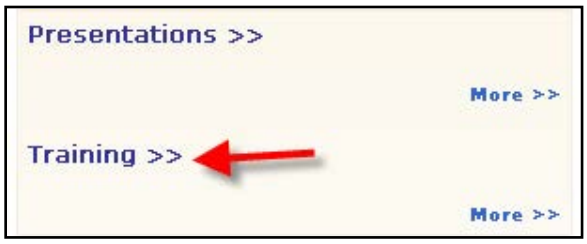
3.5.1 Online Training

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

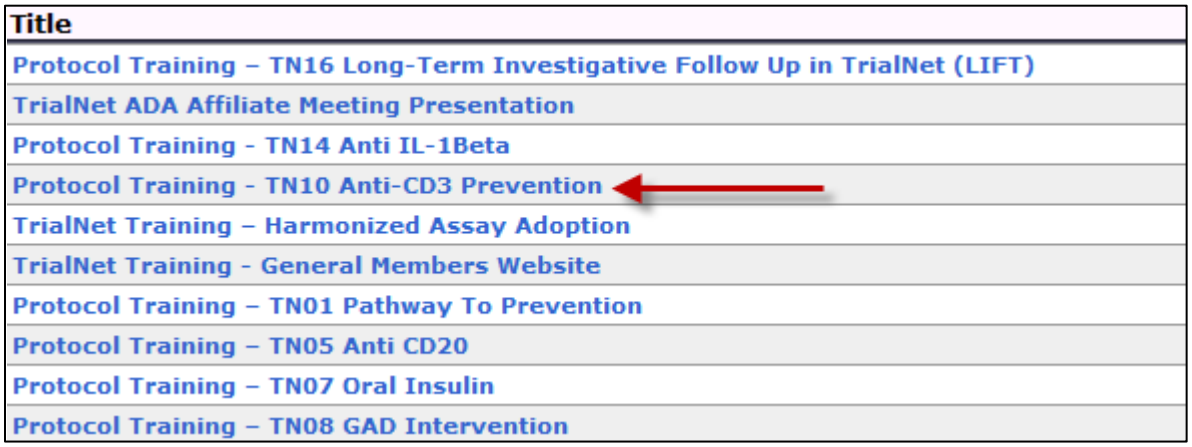
Step 1. From the main TrialNet members' website, on the left side navigation bar, click on the "TNCC Training Videos" link.



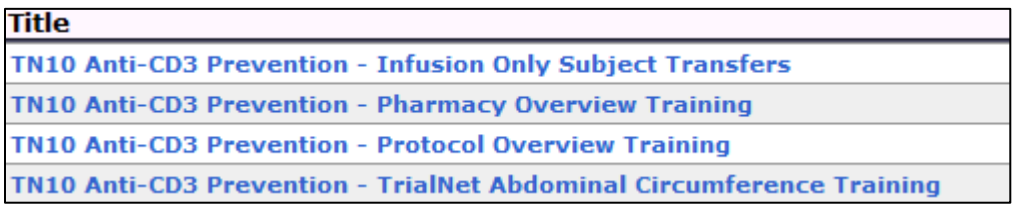
Step 2. A new window will open to the media center. Click on the "Training" link.



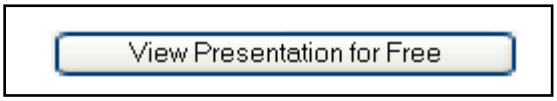
Step 3. Select the protocol/session of which you would like to view the training.



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



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) TN10 Infusion Only Subject Transfers: Provides a description on how to transfer participants to an infusion site from an enrolling site.
2) TN10 Pharmacy Training: Provides an overview of pharmacy related procedures including drug ordering, dispensing, agent return, etc
3) TN10 Protocol Overview: Provides a description of the protocol, eligibility criteria, purpose, specific aims, and details of procedures.
4) TN10 Abdominal Circumference Training: Detailed description on how to measure abdominal circumference for data collection.

3.5.2 Study Certification Quiz

The TN10 Certification Quiz is available online and can be completed by all individuals listed in roles on the Site Delegation Log requiring knowledge of study procedures. Once the certification quiz has been completed the site can request the answers from their clinical center to review.

3.6 Statement of Investigator, Form FDA 1572

The FDA 1572 Statement of Investigator should be completed by all sites participating in studies with an Investigational New Drug (IND). An original, hard copy of the form should be mailed to the TNCC protocol CRA at 3650 Spectrum Blvd, Ste 100, Tampa, FL 33612, USA. A copy should be placed in the regulatory binder at the site.

3.6.1 Updating the 1572:

The form should be updated if there is a change in the Principal Investigator or Sub-investigators at the site. A new FDA 1572 does not need to be completed for minor changes at a site such as address changes.

Any time a site updates the 1572, an original, hard copy should be mailed to the TNCC, and a scanned copy should be placed in the regulatory binder.

3.6.2 Who to include in Section 6:

The FDA 1572 section 6 should include all Sub-investigators who will be assisting the investigator in the conduct of the study. FDA's regulation 21 CFR 312.3(b) states: "In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. 'Sub-investigator' includes any other individual member of that team." 21 CFR 312.53(c)(1)(viii) requires the investigator to provide "a list of the names of the sub-investigators (e.g., research fellows, residents) who will be assisting the investigator in the conduct of the investigation(s)."

Additional clarification in the *FDA Information Sheet Guidance for Sponsors, Clinical Investigators and IRBs* states that "the purpose of Section #6 is to capture information about individuals who, as part of an investigative team, will assist the investigator and make a direct and significant contribution to the data. The decision to list an individual in Section #6 depends on his/her level of responsibility (i.e., whether he/she is performing significant clinical investigation-related duties). In general, if an individual is directly involved in the performance of procedures required by the protocol, and the collection of data, that person should be listed on the 1572. For example, if the protocol notes that each subject needs to visit a specified internist who will perform a full physical to qualify subjects for the clinical investigation, that internist should be listed in Section #6."

For additional information regarding the completion of the FDA 1572, please reference the *Information Sheet Guidance for Sponsors, Clinical Investigators and IRBs* document www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0406-gdl.pdf or contact your protocol CRA.

3.7 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.

3.8 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:

3.8.1 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).

3.8.2 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.

3.8.3 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.

3.8.4 New Primary Site Coordinator

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

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

3.8.5 Changes in Site PI

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

1. IRB/ERB modification recognizing the new PI will be continuing the study
2. Confidentiality Form for new PI
3. Documentation of human subjects research training for new PI
4. Signed and dated copy of PI's CV
5. New User Form for new PI (if applicable)
6. Updated Site Delegation Log signed by the new PI.
7. Site should ensure W9/W8 BEN on file at the TNCC still reflects the preferred payment information.
8. FDA 1572 should be revised to reflect the new PI
9. New PI should complete a Duality of Interest form (if not previously completed).
10. If the previous PI is no longer at the site, the Site Delegation Log should be updated and a Remove User form should be submitted (see section 3.8.2).

3.8.6 End Participation With TrialNet

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

Step 1. Site should notify their clinical center and the TNCC protocol CRA of their intention to cease participation with TrialNet.

Step 2. The site should notify their IRB/ERB of the study closure and indicate that all active participants should be transferred to the site's clinical center for follow-up.

Step 3. The site should submit the IRB/ERB Final Closure documentation and submit the Request to End Participation with TrialNet form to the TNCC.

4. RECRUITMENT PROCEDURES AND STRATEGIES

4.1 Recruitment Goals

140-170 subjects over 5 years

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:

1. Participant in TrialNet Natural History Study (TN01) and thus a relative of a proband** with T1D.
2. Between the ages of 1-45 years at time of enrollment in TN01 and age ≥ 8 at time of randomization in this trial.
3. Subject (or parent or legal guardian) is willing to provide Informed Consent Form.
4. An abnormal glucose tolerance by OGTT confirmed within 7 weeks of baseline (visit 0)
    a. Fasting plasma glucose ≥ 110 mg/dL, and < 126 mg/dl*
    or
    b. 2 hour plasma glucose ≥ 140 mg/dL, and < 200 mg/dl
    or
    c. 30, 60, or 90 minute value on OGTT ≥200mg/dl
5. The participant must confirm positive for any combination of two diabetes-related autoantibodies on two occasions. This confirmation of two positive autoantibodies must occur within the six months prior to study drug administration, but does not need to involve the same two autoantibodies. The autoantibodies that will be confirmed are anti-GAD65, anti-ICA512, anti-insulin (MIAA), ZnT8 and/or ICA.
6. Weigh at least 26 kg at randomization.
7. If participant is female with reproductive potential, she must have a negative pregnancy test on Day 0 and be willing to avoid pregnancy for at least one year from randomization.
8. If participant is male, he must be willing to avoid pregnancy in any partners for at least one year from randomization.
9. Willing and medically acceptable to postpone live vaccine immunizations for one year after treatment.
10. Willing to forego other forms of experimental treatment during the study.

* Fasting glucose levels of 110-125 mg/dL qualify subjects as having abnormal glucose tolerance in this protocol as it reflects the criteria used for entry into the DPT-1 (33) study and the DPT-1 data was used for the calculation of diabetes risk for this trial. Using data for individuals with Type 2 diabetes, the ADA uses a different glucose range to define impaired fasting glucose (34).

**A proband is an individual diagnosed with diabetes before age 40 and started on insulin therapy within one year of diagnosis, or if subjects with probands considered to have type 1 diabetes by their physician who do not meet this definition, the TrialNet Eligibility Committee for the TrialNet Natural History Study (TN01) must have approved enrollment in TN01.

Exclusion Criteria:

1. Diabetes, or have a screening OGTT with:
    a. Fasting plasma glucose ≥ 126 mg/dL, or
    b. 2 hour plasma glucose ≥ 200 mg/dL
2. Lymphopenia (< 1000 lymphocytes/µL).
3. Neutropenia (< 1500 PMN/µL).
4. Thrombocytopenia (< 150,000 platelets/µL).
5. Anemia (Hgb < 10 grams/deciliter [g/dL]).
6. Total bilirubin >1.5 x upper limit of normal (ULN).
7. AST or ALT >1.5 x ULN.
8. INR > 0.1 above the upper limit of normal at the participating center's laboratory.
9. Chronic active infection other than localized skin infections.
10. A positive PPD test.
11. Vaccination with a live virus within 8 weeks of randomization
12. Vaccination with a killed virus within 4 weeks of randomization.
13. A history of infectious mononucleosis within the 3 months prior to enrollment.
14. Laboratory or clinical evidence of acute infection with EBV or CMV.
15. Serological evidence of current or past HIV, Hepatitis B or Hepatitis C infection.
16. Be currently pregnant or lactating, or anticipate getting pregnant.
17. Chronic use of steroids or other immunosuppressive agents.
18. A history of asthma or atopic disease requiring chronic treatment.
19. Untreated hypothyroidism or active Graves' disease at randomization.
20. Current use of non-insulin pharmaceuticals that affect glycemic control.
21. Prior OKT®3 or other anti-CD3 treatment.
22. Administration of a monoclonal antibody within the year before randomization.
23. Participation in any type of therapeutic drug or vaccine clinical trial within the 12 weeks before randomization.
24. Any condition that, in the opinion of the investigator, would interfere with the study conduct or the safety of the subject.

4.4 Exceptions to Questions Regarding Eligibility Criteria

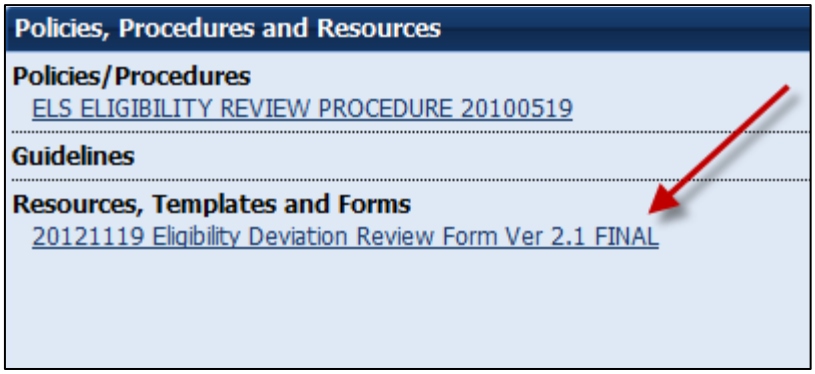
The TrialNet Coordinating Center will be responsible for initially reviewing and adjudicating any instances where eligibility is unclear. If following this initial review eligibility is still unclear, the TrialNet Eligibility Committee will review and adjudicate the situation.

4.4.1 Procedures for submission to the TrialNet Eligibility Committee

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

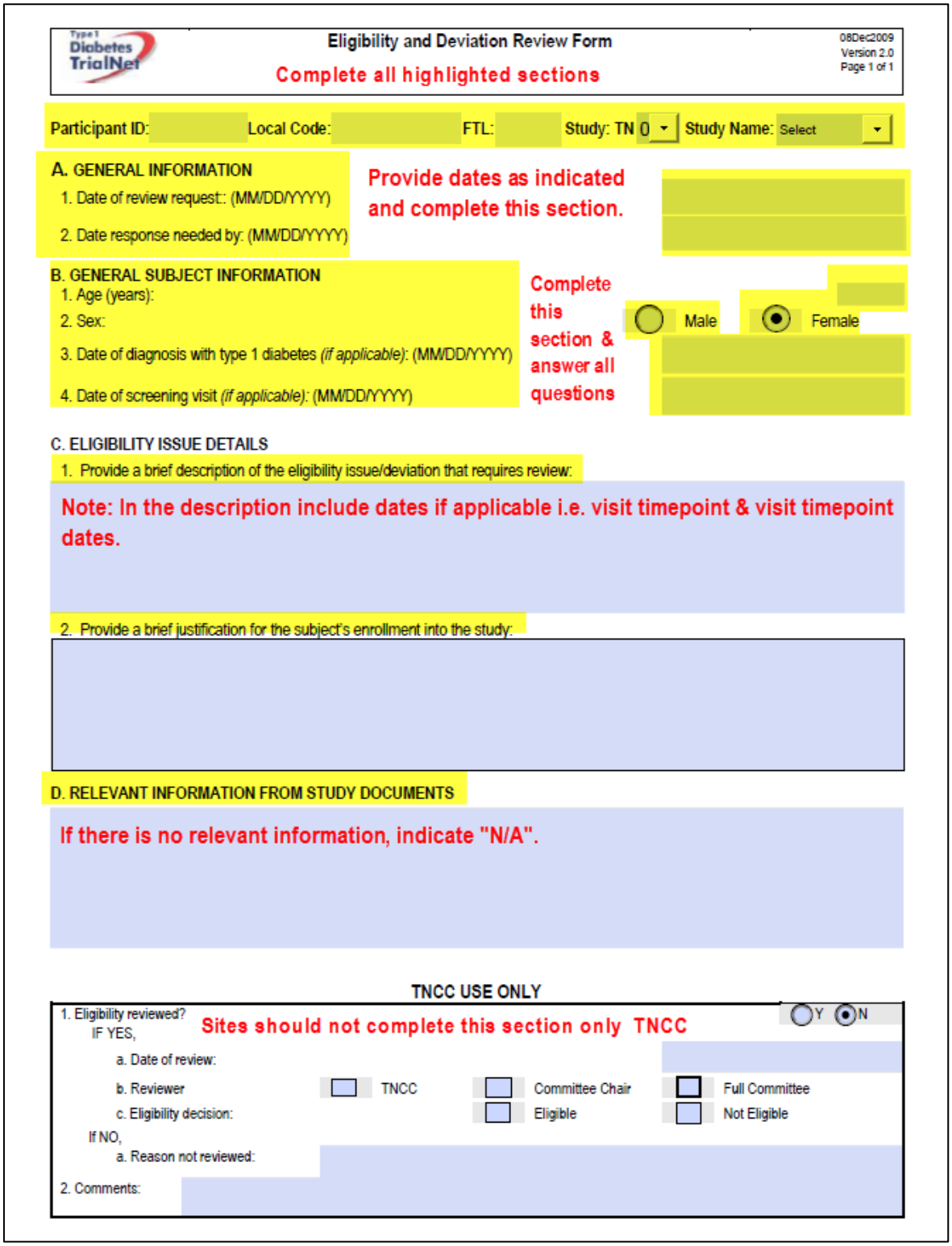
Step 1. Contact the TNCC CRA to review the question or matter regarding eligibility if unclear in the protocol

Step 2. If TNCC CRA unable to clarify proceed to complete the Eligibility Deviation Review Form. This form is located in the Eligibility Subcommittee page under the Policies, Procedures and Resources Portlet.



Step 3. Complete all portions of this form except the section titled “TNCC Only” and email back to the lead TNCC CRA and cc Julie Ford.

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



Eligibility and Deviation Review Form

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Complete all highlighted sections

Participant ID: Local Code: FTL: Study: TN 0 Study Name: Select

A. GENERAL INFORMATION

1. Date of review request:: (MM/DD/YYYY)
2. Date response needed by: (MM/DD/YYYY)

Provide dates as indicated and complete this section.

B. GENERAL SUBJECT INFORMATION

1. Age (years):
2. Sex:
3. Date of diagnosis with type 1 diabetes *(if applicable)*: (MM/DD/YYYY)
4. Date of screening visit *(if applicable)*: (MM/DD/YYYY)

Complete this section & answer all questions

Male Female

C. ELIGIBILITY ISSUE DETAILS

1. Provide a brief description of the eligibility issue/deviation that requires review:

Note: In the description include dates if applicable i.e. visit timepoint & visit timepoint dates.

2. Provide a brief justification for the subject's enrollment into the study:

D. RELEVANT INFORMATION FROM STUDY DOCUMENTS

If there is no relevant information, indicate "N/A".

TNCC USE ONLY

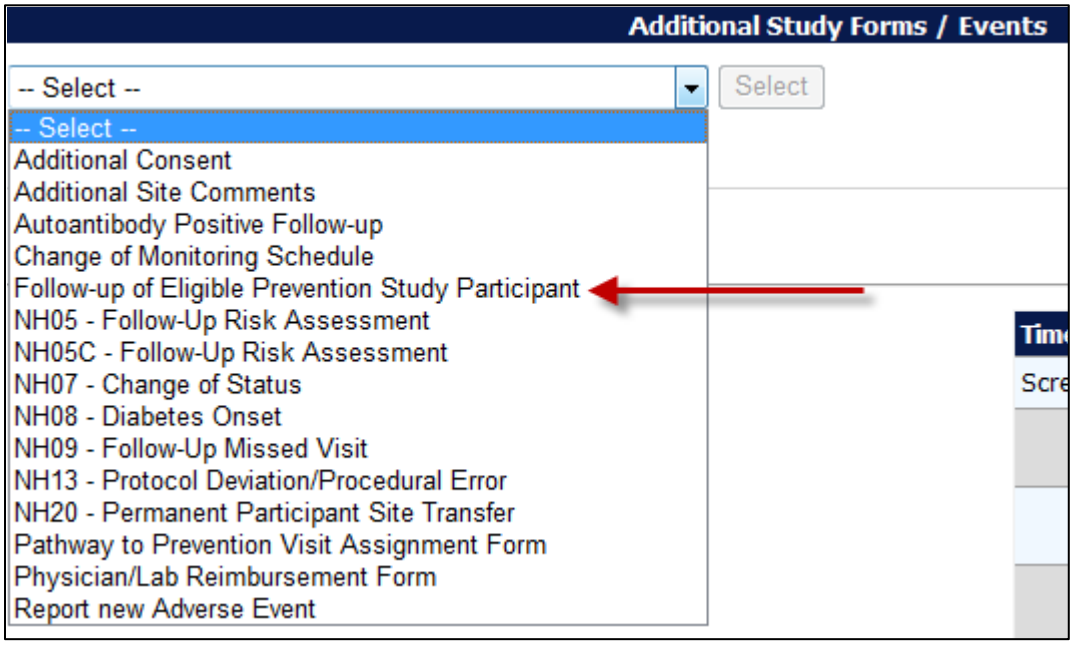
1. Eligibility reviewed? Y N
   IF YES, Sites should not complete this section only TNCC
   a. Date of review:
   b. Reviewer TNCC Committee Chair Full Committee
   c. Eligibility decision: Eligible Not Eligible
   If NO,
   a. Reason not reviewed:
2. Comments:

4.5 Follow-up of Eligible Study Participant

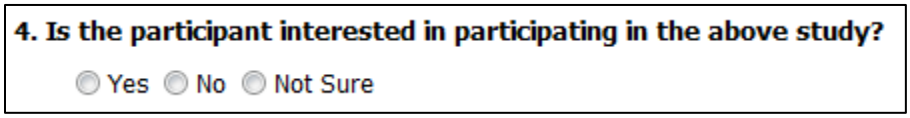
Once a participant has been asked to participate in this study please complete the Follow Up of Eligible Study Participant eCRF. *(Please Note: For the corresponding assessment tool please see section 5.)*

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

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



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.



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

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

Reasons	Please rank the importance of this reason for the participant declining the study
☐ 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 TN10 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 TN10 laboratory Manual of Operations.

5.1 Visit -1 Screening

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Order any supplies needed for the study procedures through the online Fisher BioServices Supply Ordering System. See section 6.4 for a list of supplies required for each specimen collection.	NA	NA
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc). Refer to instructions above for location of visit checklists.	NA	NA
Pre-visit	Remind the participant that they need to be fasting for this visit.	NA	NA
At Visit	Administer the screening consent and if applicable screening assent, local HIV screening consent, and local HIPAA form.	Consent & Assent	Screening Informed Consent Verification
At Visit	Register the participant in the online system	NA	NA
At Visit	Administer the volunteer survey. Coordinator should review the survey with the participant and parents (if applicable) taking special care to review any incorrect answers. (Screening or Baseline visit)	Volunteer Understanding Assessment	NA
At Visit	Collect participant’s medical history	Complete Medical History	Screening Medical History
At Visit	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	ConMeds	Concomitant Medication
At Visit	Conduct a physical exam	Complete PE	Physical Exam
At Visit	Conduct a PPD test and remind the participant that the test needs to be read between 48-72 hours.	Local PPD Source	NA
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Conduct an OGTT test*	Local OGTT Source	Screening Specimen Collection

At Visit	**Local** lab collection: 1. CBC with differential 2. INR	Lab Results signed and dated by MD or delegated personnel	Local Lab Results
At Visit	**Central** lab collection: 1. Anti-teplizumab Response 2. HIV/Hep B/Hep C Serology 3. EBV/CMV Viral Serology 4. EBV/CMV Viral Load 5. HbA1c 6. Chemistries and Liver Function	Signed and dated printout of specimen collection form	Screening Specimen Collection
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

* For specific instructions on how to conduct an OGTT please see appendix B. (For the location of all appendices please reference section 11.1.3)

5.1.1 Screen Failures

If the participant is a screen failure the site coordinator should do the following:

Step 1. Enter all data collected for the screening visit into the eCRF.

Step 2. Complete all tracking forms for the baseline visit as "Not Done". "Other" should be checked and "Screen Failure" should be entered in the comment box.

Step 3. Complete "Pre-Randomization Exit" form under "Additional Study Forms".
Note: Participant will return to the Pathway to Prevention study for monitoring.

Step 4. Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.

5.1.2 Rescreen Procedures

Rescreen within 30 days:

If they are eligible for rescreening within 30 days of the initial screening visit, the following procedures are required:

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Site should review subject's CBC, Chemistries, EBV and CMV serologies from the subject's initial TN10 screening visit. If subject had a normal CBC and normal chemistries along with negative EBV and CMV serologies, they will only need to repeat the OGTT and the viral load.	NA	NA
At Visit	Collect participant's medical history	Interim Medical History	Interim Medical History
At Visit	Conduct a complete physical exam	Interim PE	Interim Physical Exam
At Visit	Visit lab collection: **The following collections are only required if abnormal at initial screening visit:** 1. CBC with differential (local) 2. Chemistries (central) 3. Liver Function (central) 4. EBV/CMV Viral Serology (central) The following collections are **required repeat** collections: 1. EBV/CMV Viral Load (central)	Signed and dated printout of specimen collection form and Local Lab Results	PRN Specimen Collection
At Visit	Conduct an OGTT	Local OGTT Source and Signed Specimen Collection Form	PRN Specimen Collection
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
Post Visit	Complete the "Change of Status" PRN form in the online system to reactivate participant	NA	Change of Status (PRN)
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s).	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

Please note: Previous screen failure data should be transferred into a PRN form with the exception of specimen collections. New screening visit data should be entered into the screening eCRFs. Rescreen specimen collections should be entered in a PRN form.

Rescreen after 30 days:

If participant becomes eligible to rescreen outside of 30 days a full screening visit is required.

5.2 Visit 0 Baseline:

Window: Within 7 weeks after confirmatory OGTT

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Complete the online Registration	NA	Registration Form
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, etc).	NA	NA
At Visit	Administer the intervention consent (and assent if participant is under the age of 18), (if not completed at screening visit).	Consent	NA
At Visit	Administer the volunteer survey (if not done at screening visit). Coordinator should review the survey with the participant and parents (if applicable) taking special care to review any incorrect answers.	Volunteer Understanding Assessment	NA
At Visit	Collect participant's interim medical history	Interim Medical History	Interim Medical History
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Conduct a complete physical exam	Interim PE	Interim Physical Exam
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher)	AE assessment	Adverse Events
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Complete EKG	EKG Output	EKG
At Visit	**Local** lab collection: 1. CBC with differential 2. Chemistries 3. INR 4. Liver Function	Lab Results signed and dated by MD	Local Lab Results
At Visit	**Central** lab collection: 1. PK Sample* 2. Mechanistic Assessments a. PBMC/Plasma b. RNA c. Mechanistic Serum d. HLA (if not collected in TN01)	Signed and dated printout of specimen collection form	Specimen Collection

At Visit	Administer first dose of study agent	Study Drug Administration	Study Drug Administration
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the SMS Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

* Pre-Infusion PK samples will be done on the first 12 subjects in each of the age strata: ≥16, 12-15, and 8-11. For specific instructions on how to collect PK samples please see the Laboratory Manual of Operations.

5.3 Visit 1 (Day 1) through Visit 4 (Day 4):

Window: Next day

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, etc).	NA	NA
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher)	AE assessment	Adverse Events
At Visit	**Local** lab collection: 1. CBC with differential 2. Chemistries 3. INR 4. Liver Function	Lab Results signed and dated by MD	Local Lab Results
At Visit	Administer study agent	Study Drug Administration	Study Drug Administration
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.4 Visit 5 Day 5:

Window: + 1 Day from Visit 4 Day 4

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared	NA	NA

	for visit (procedures, etc).		
At Visit	Collect participant's interim medical history	Interim Medical History	Interim Medical History
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher)	AE assessment	Adverse Events
At Visit	Conduct a complete physical exam	Interim PE	Interim Physical Exam
At Visit	**Local** lab collection: 1. CBC with differential 2. Chemistries 3. INR 4. Liver Function	Lab Results signed and dated by MD	Local Lab Results
At Visit	Administer study agent	Study Drug Administration	Study Drug Administration
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.5 Visit 6 (Day 6):

Window: Next day

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, etc).	NA	NA
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher)	AE assessment	Adverse Events
At Visit	**Local** lab collection: 1. CBC with differential 2. Chemistries 3. Liver Function	Lab Results signed and dated by MD	Local Lab Results
At Visit	Administer study agent	Study Drug Administration	Study Drug Administration
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.6 Visit 7 (Day 7):

Window: Next day

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, etc).	NA	NA
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher)	AE assessment	Adverse Events
At Visit	Administer study agent	Study Drug Administration	Study Drug Administration
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.7 Visit 8 (Day 8):

Window: Next day

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, etc).	NA	NA
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher)	AE assessment	Adverse Events
At Visit	**Local** lab collection: 1. CBC with differential	Lab Results signed and dated by MD	Local Lab Results
At Visit	Administer study agent	Study Drug Administration	Study Drug Administration
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.8 Visit 9 (Day 9):

Window: Next day

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared	NA	NA

	for visit (procedures, etc).		
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher)	AE assessment	Adverse Events
At Visit	Administer study agent	Study Drug Administration	Study Drug Administration
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.9 Visit 10 (Day 10):

Window: Next day

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, etc).	NA	NA
At Visit	Collect participant's interim medical history	Interim Medical History	Interim Medical History
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher)	AE assessment	Adverse Events
At Visit	Conduct a complete physical exam	Interim PE	Interim Physical Exam
At Visit	**Central** lab collection: 1. PK Sample*	Signed and dated printout of specimen collection form	Specimen Collection
At Visit	Administer study agent	Study Drug Administration	Study Drug Administration
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s).	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

* Pre-Infusion PK samples will be done on the first 12 subjects in each of the age strata: ≥16, 12-15, and 8-11.

5.10 Visit 11 (Day 11):

Window: Next day

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, etc).	NA	NA
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher)	AE assessment	Adverse Events
At Visit	**Local** lab collection: 1. CBC with differential 2. Chemistries 3. INR 4. Liver Function	Lab Results signed and dated by MD	Local Lab Results
At Visit	**Central** lab collection: 1. PK Sample*	Signed and dated printout of specimen collection form	Specimen Collection
At Visit	Administer study agent	Study Drug Administration	Study Drug Administration
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s).	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

* Pre-Infusion PK samples will be done on the first 12 subjects in each of the age strata: ≥16, 12-15, and 8-11.

5.11 Visit 12 (Day 12):

Window: Next day

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, etc).	NA	NA

At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher)	AE assessment	Adverse Events
At Visit	**Central** lab collection: 1. PK Sample*	Signed and dated printout of specimen collection form	Specimen Collection
At Visit	Administer study agent	Study Drug Administration	Study Drug Administration
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s).	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

* Pre-Infusion PK samples will be done on the first 12 subjects in each of the age strata: ≥16, 12-15, and 8-11.

5.12 Visit 13 (Day 13):

Window: Next day

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, etc).	NA	NA
At Visit	Collect participant's interim medical history	Interim Medical History	Interim Medical History
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Conduct a complete physical exam	Interim PE	Interim Physical Exam
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher)	AE assessment	Adverse Events
At Visit	**Local** lab collection: 1. CBC with differential 2. Chemistries 3. INR 4. Liver Function	Lab Results signed and dated by MD	Local Lab Results

At Visit	**Central** lab collection: 1. PK Sample*	Signed and dated printout of specimen collection form	Specimen Collection
At Visit	Administer study agent	Study Drug Administration	Study Drug Administration
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the SMS Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

* Pre-Infusion PK samples will be done on the first 12 subjects in each of the age strata: ≥16, 12-15, and 8-11.

5.13 Visit 14 (Day 20):

Window: +/- 2 days

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc). Refer to instructions above for location of visit checklists.	NA	NA
At Visit	Collect interim medical history	Complete Medical History	Medical History
At Visit	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	ConMeds	Concomitant Medication
At Visit	Conduct a complete physical exam	Complete PE	Physical Exam
At Visit	**Local** lab collection: 1. CBC with differential	Lab Results signed and dated by MD	Local Lab Results
At Visit	**Central** lab collection: 1. EBV/CMV Viral Load 2. Mechanistic Assessments a. PBMC/Plasma b. RNA	Signed and dated printout of specimen collection form	Specimen Collection
Post Visit	Enter data collected on source documents into the e-	NA	NA

	CRF's online.		
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.14 Week 4 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Phone Contact	Phone Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.15 Visit 15 (Week 6):

Window: +/- 4 days

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc). Refer to instructions above for location of visit checklists.	NA	NA
At Visit	Collect participant's interim medical history	Interim Medical History	Interim Medical History
At Visit	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	ConMeds	Concomitant Medication
At Visit	Conduct a complete physical exam	Complete PE	Physical

			Exam
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	**Local** lab collection: 1. CBC with differential	Lab Results signed and dated by MD	Local Lab Results
At Visit	**Central** lab collection: 1. Chemistries 2. Liver Function 3. EBV/CMV Viral Load	Signed and dated printout of specimen collection form	Specimen Collection
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.16 Month 2 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Phone Contact	Phone Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.17 Visit 16 (Month 3):

Window: +/- 3 Weeks

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc). Refer to instructions above for location of visit checklists.	NA	NA
Pre-visit	Remind the participant that they need to be fasting for this visit.	NA	NA
At Visit	Collect participant's interim medical history	Interim Medical History	Interim Medical History
At Visit	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	ConMeds	Concomitant Medication
At Visit	Conduct a directed/ limited physical exam	PE Source	Physical Exam
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Conduct an OGTT	Local OGTT Source	Specimen Collection
At Visit	**Local** lab collection: 1. CBC with differential	Lab Results signed and dated by MD	Local Lab Results
At Visit	**Central** lab collection: 1. Anti-teplizumab Response 2. EBV/CMV Viral Load 3. HbA1c 4. Mechanistic Assessments a. PBMC/Plasma	Signed and dated printout of specimen collection form	Specimen Collection
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.18 Month 4 and 5 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact

During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Phone Contact	Phone Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.19 Visit 17 (Month 6):

Window: +/- 3 Weeks

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc). Refer to instructions above for location of visit checklists.	NA	NA
Pre-visit	Remind the participant that they need to be fasting for this visit.	NA	NA
At Visit	Collect participant's interim medical history	Interim Medical History	Interim Medical History
At Visit	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	ConMeds	Concomitant Medication
At Visit	Conduct a directed/limited physical exam	PE Source	Physical Exam
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Conduct an OGTT	Local OGTT Source	Specimen Collection
At Visit	**Local** lab collection: 1. CBC with differential	Lab Results signed and dated by MD	Local Lab Results
At Visit	**Central** lab collection: 1. Chemistries 2. Liver Function 3. HbA1c 4. Mechanistic Assessments a. PBMC/Plasma b. Mechanistic Serum	Signed and dated printout of specimen collection form	Specimen Collection
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample	NA	NA

	into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.		
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.20 Months 7 and 8 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Phone Contact	Phone Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.21 Month 9 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue and irritability.	Phone Contact	Phone Contact
During the Call	Schedule random glucose sample collection.	NA	NA
Post Call	**Central** lab collection: 1. Random Glucose*	Signed and dated	Specimen Collection

	Note: If specimen is collected at a lab other than the site, specimen should be sent to the site first, and should then be shipped to the Beta Cell/Biochemistry Core lab.	printout of specimen collection form	
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Call	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

**Participants with symptoms or random glucose >200mg/dl will undergo fasting glucose or OGTT evaluation.*

5.22 Months 10 and 11 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Phone Contact	Phone Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.23 Visit 18 (Month 12):

Window: +/- 3 Weeks

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc). Refer to instructions above for location of visit checklists.	NA	NA
Pre-visit	Remind the participant that they need to be fasting	NA	NA

	for this visit.		
At Visit	Collect participant's interim medical history	Interim Medical History	Interim Medical History
At Visit	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	ConMeds	Concomitant Medication
At Visit	Conduct a complete physical exam	Complete PE	Physical Exam
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Conduct an OGTT	Local OGTT Source	Specimen Collection
At Visit	**Local** lab collection: 1. CBC with differential	Lab Results signed and dated by MD	Local Lab Results
At Visit	**Central** lab collection: 1. Chemistries 2. Liver Function 3. EBV/CMV Viral Serology 4. EBV/CMV Viral Load 5. HbA1c 6. Mechanistic Assessments a. RNA b. Mechanistic Serum	Signed and dated printout of specimen collection form	Specimen Collection
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.24 Months 13 and 14 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is	Phone Contact	Concomitant Medication

	added.		
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Phone Contact	Phone Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.25 Month 15 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue and irritability.	Phone Contact	Phone Contact
During the Call	Schedule random glucose sample collection.	NA	NA
Post Call	**Central** lab collection: 1. Random Glucose* *Note: If specimen is collected at a lab other than the site, specimen should be sent to the site first, and should then be shipped to the Beta Cell/Biochemistry Core lab.*	Signed and dated printout of specimen collection form	Specimen Collection
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Call	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

** Participants with symptoms or random glucose >200mg/dl will undergo fasting glucose or OGTT evaluation.*

5.26 Months 16 and 17 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Phone Contact	Phone Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.27 Visit 19 (Month 18):

Window: +/- 3 Weeks

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc). Refer to instructions above for location of visit checklists.	NA	NA
Pre-visit	Remind the participant that they need to be fasting for this visit.	NA	NA
At Visit	Collect participant's interim medical history	Interim Medical History	Interim Medical History
At Visit	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	ConMeds	Concomitant Medication
At Visit	Conduct a directed/limited physical exam	PE Source	Physical Exam
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Conduct an OGTT	Local OGTT Source	Specimen Collection
At Visit	**Local** lab collection: 1. CBC with differential	Lab Results signed and dated by MD	Local Lab Results
At Visit	**Central** lab collection: 1. HbA1c 2. Mechanistic Assessments	Signed and dated printout of	Specimen Collection

	a. PBMC/Plasma b. Mechanistic Serum	specimen collection form	
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.28 Months 19 and 20 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Phone Contact	Phone Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.29 Month 21 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During	Ask the subject regarding the presence or absence of	Phone	Phone

the Call	blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue and irritability.	Contact	Contact
During the Call	Schedule random glucose sample collection.	NA	NA
Post Call	**Central** lab collection: 1. Random Glucose* *Note: If specimen is collected at a lab other than the site, specimen should be sent to the site first, and should then be shipped to the Beta Cell/Biochemistry Core lab.*	Signed and dated printout of specimen collection form	Specimen Collection
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Call	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

** Participants with symptoms or random glucose >200mg/dl will undergo fasting glucose or OGTT evaluation.*

5.30 Months 22 and 23 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Phone Contact	Phone Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.31 Visit 20 (Month 24):

Window: +/- 3 Weeks

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc). Refer to instructions above for location of visit checklists.	NA	NA
Pre-visit	Remind the participant that they need to be fasting for this visit.	NA	NA
At Visit	Collect participant's interim medical history	Interim Medical History	Interim Medical History
At Visit	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	ConMeds	Concomitant Medication
At Visit	Conduct a complete physical exam	Complete PE	Physical Exam
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Conduct an OGTT	Local OGTT Source	Specimen Collection
At Visit	**Local** lab collection: 1. CBC with differential	Lab Results signed and dated by MD	Local Lab Results
At Visit	**Central** lab collection: 1. Chemistries 2. Liver Function 3. EBV/CMV Viral Serology 4. EBV/CMV Viral Load 5. HbA1c 6. Mechanistic Assessments a. Mechanistic Serum	Signed and dated printout of specimen collection form	Specimen Collection
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.32 Months 25 and 26 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Phone Contact	Phone Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.33 Month 27 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue and irritability.	Phone Contact	Phone Contact
During the Call	Schedule random glucose sample collection.	NA	NA
Post Call	**Central** lab collection: 1. Random Glucose* *Note: If specimen is collected at a lab other than the site, specimen should be sent to the site first, and should then be shipped to the Beta Cell/Biochemistry Core lab.*	Signed and dated printout of specimen collection form	Specimen Collection
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA

Post Call	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

** Participants with symptoms or random glucose >200mg/dl will undergo fasting glucose or OGTT evaluation.*

5.34 Months 28 and 29 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Phone Contact	Phone Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.35 Visit 21 (Month 30):

Window: +/- 3 Weeks

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc). Refer to instructions above for location of visit checklists.	NA	NA
Pre-visit	Remind the participant that they need to be fasting for this visit.	NA	NA
At Visit	Collect participant's interim medical history	Interim Medical History	Interim Medical History
At Visit	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	ConMeds	Concomitant Medication
At Visit	Conduct a directed/limited physical exam	PE Source	Physical Exam

At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Conduct an OGTT	Local OGTT Source	Specimen Collection
At Visit	**Central** lab collection: 1. HbA1c 2. Mechanistic Assessments a. PBMC/Plasma b. Mechanistic Serum	Signed and dated printout of specimen collection form	Specimen Collection
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.36 Months 31 and 32 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Phone Contact	Phone Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.37 Month 33 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue and irritability.	Phone Contact	Phone Contact
During the Call	Schedule random glucose sample collection.	NA	NA
Post Call	**Central** lab collection: 1. Random Glucose* *Note: If specimen is collected at a lab other than the site, specimen should be sent to the site first, and should then be shipped to the Beta Cell/Biochemistry Core lab.*	Signed and dated printout of specimen collection form	Specimen Collection
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Call	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

** Participants with symptoms or random glucose >200mg/dl will undergo fasting glucose or OGTT evaluation.*

5.38 Months 34 and 35 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During	Ask the subject regarding the presence or absence of	Phone	Phone

the Call	blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Contact	Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.39 Visit 22 (Month 36):

Window: +/- 3 Weeks

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc). Refer to instructions above for location of visit checklists.	NA	NA
Pre-visit	Remind the participant that they need to be fasting for this visit.	NA	NA
At Visit	Collect participant's interim medical history	Interim Medical History	Interim Medical History
At Visit	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	ConMeds	Concomitant Medication
At Visit	Conduct a complete physical exam	Complete PE	Physical Exam
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Conduct an OGTT	Local OGTT Source	Specimen Collection
At Visit	**Local** lab collection: 1. CBC with differential	Lab Results signed and dated by MD	Local Lab Results
At Visit	**Central** lab collection: 1. Chemistries 2. Liver Function 3. EBV/CMV Viral Serology 4. EBV/CMV Viral Load 5. HbA1c 6. Mechanistic Assessments a. Mechanistic Serum	Signed and dated printout of specimen collection form	Specimen Collection
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA

Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.40 Months 37 and 38 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Phone Contact	Phone Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.41 Month 39 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue and irritability.	Phone Contact	Phone Contact
During the Call	Schedule random glucose sample collection.	NA	NA
Post Call	**Central** lab collection: 1. Random Glucose* *Note: If specimen is collected at a lab other than the site, specimen should be sent to the site first, and should then be shipped to the Beta Cell/Biochemistry Core lab.*	Signed and dated printout of specimen collection form	Specimen Collection

Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Call	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

** Participants with symptoms or random glucose >200mg/dl will undergo fasting glucose or OGTT evaluation.*

5.42 Months 40 and 41 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Phone Contact	Phone Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.43 Visit 23 (Month 42):

Window: +/- 3 Weeks

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc). Refer to instructions above for location of visit checklists.	NA	NA
Pre-visit	Remind the participant that they need to be fasting for this visit.	NA	NA
At Visit	Collect participant's interim medical history	Interim Medical	Interim Medical

		History	History
At Visit	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	ConMeds	Concomitant Medication
At Visit	Conduct a directed/limited physical exam	PE Source	Physical Exam
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Conduct an OGTT	Local OGTT Source	Specimen Collection
At Visit	**Central** lab collection: 1. HbA1c 2. Mechanistic Assessments a. PBMC/Plasma b. Mechanistic Serum	Signed and dated printout of specimen collection form	Specimen Collection
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.44 Months 43 and 44 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Phone Contact	Phone Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.45 Month 45 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue and irritability.	Phone Contact	Phone Contact
During the Call	Schedule random glucose sample collection.	NA	NA
Post Call	**Central** lab collection: 1. Random Glucose* *Note: If specimen is collected at a lab other than the site, specimen should be sent to the site first, and should then be shipped to the Beta Cell/Biochemistry Core lab.*	Signed and dated printout of specimen collection form	Specimen Collection
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Call	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

** Participants with symptoms or random glucose >200mg/dl will undergo fasting glucose or OGTT evaluation.*

5.46 Months 46 and 47 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact

During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Phone Contact	Phone Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.47 Visit 24 (Month 48):

Window: +/- 3 Weeks

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc). Refer to instructions above for location of visit checklists.	NA	NA
Pre-visit	Remind the participant that they need to be fasting for this visit.	NA	NA
At Visit	Collect participant's interim medical history	Interim Medical History	Interim Medical History
At Visit	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	ConMeds	Concomitant Medication
At Visit	Conduct a complete physical exam	Complete PE	Physical Exam
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Conduct an OGTT	Local OGTT Source	Specimen Collection
At Visit	**Local** lab collection: 1. CBC with differential	Lab Results signed and dated by MD	Local Lab Results
At Visit	**Central** lab collection: 1. Chemistries 2. Liver Function 3. EBV/CMV Viral Serology 4. EBV/CMV Viral Load 5. HbA1c 6. Mechanistic Assessments a. Mechanistic Serum	Signed and dated printout of specimen collection form	Specimen Collection
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA

Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.48 Months 49 and 50 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Phone Contact	Phone Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.49 Month 51 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue and irritability.	Phone Contact	Phone Contact
During the Call	Schedule random glucose sample collection.	NA	NA
Post Call	**Central** lab collection:	Signed and	Specimen

	1. Random Glucose* *Note: If specimen is collected at a lab other than the site, specimen should be sent to the site first, and should then be shipped to the Beta Cell/Biochemistry Core lab.*	dated printout of specimen collection form	Collection
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Call	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

** Participants with symptoms or random glucose >200mg/dl will undergo fasting glucose or OGTT evaluation.*

5.50 Months 52 and 53 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Phone Contact	Phone Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.51 Visit 25 (Month 54):

Window: +/- 3 Weeks

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc). Refer to instructions above for location of visit checklists.	NA	NA

Pre-visit	Remind the participant that they need to be fasting for this visit.	NA	NA
At Visit	Collect participant's interim medical history	Interim Medical History	Interim Medical History
At Visit	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	ConMeds	Concomitant Medication
At Visit	Conduct a directed/limited physical exam	PE Source	Physical Exam
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Conduct an OGTT	Local OGTT Source	Specimen Collection
At Visit	**Central** lab collection: 1. HbA1c 2. Mechanistic Assessments a. PBMC/Plasma b. Mechanistic Serum	Signed and dated printout of specimen collection form	Specimen Collection
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.52 Months 55 and 56 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Phone Contact	Phone Contact
Post Call	Enter data collected on source documents into the e-	NA	NA

	CRF's online.		
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.53 Month 57 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue and irritability.	Phone Contact	Phone Contact
During the Call	Schedule random glucose sample collection.	NA	NA
Post Call	**Central** lab collection: 1. Random Glucose* *Note: If specimen is collected at a lab other than the site, specimen should be sent to the site first, and should then be shipped to the Beta Cell/Biochemistry Core lab.*	Signed and dated printout of specimen collection form	Specimen Collection
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Call	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

** Participants with symptoms or random glucose >200mg/dl will undergo fasting glucose or OGTT evaluation.*

5.54 Months 58 and 59 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During	Ask if the participant had any changes in health since	Phone	Phone

the Call	last visit.	Contact	Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Phone Contact	Phone Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.55 Visit 26 (Month 60):

Window: +/- 3 Weeks

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc). Refer to instructions above for location of visit checklists.	NA	NA
Pre-visit	Remind the participant that they need to be fasting for this visit.	NA	NA
At Visit	Collect participant's interim medical history	Interim Medical History	Interim Medical History
At Visit	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	ConMeds	Concomitant Medication
At Visit	Conduct a complete physical exam	Complete PE	Physical Exam
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Conduct an OGTT	Local OGTT Source	Specimen Collection
At Visit	**Local** lab collection: 1. CBC with differential	Lab Results signed and dated by MD	Local Lab Results
At Visit	**Central** lab collection: 1. Chemistries 2. Liver Function 3. HbA1c 4. Mechanistic Assessments a. Mechanistic Serum	Signed and dated printout of specimen collection form	Specimen Collection
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample	NA	NA

	into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.		
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.56 Months 61 and 62 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Phone Contact	Phone Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.57 Month 63 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue and irritability.	Phone Contact	Phone Contact
During the Call	Schedule random glucose sample collection.	NA	NA
Post Call	**Central** lab collection: 1. Random Glucose*	Signed and dated	Specimen Collection

	Note: If specimen is collected at a lab other than the site, specimen should be sent to the site first, and should then be shipped to the Beta Cell/Biochemistry Core lab.	printout of specimen collection form	
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Call	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

** Participants with symptoms or random glucose >200mg/dl will undergo fasting glucose or OGTT evaluation.*

5.58 Months 64 and 65 Interim Phone Contact:

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Phone Contact	Phone Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.59 Visit 27 (Month 66):

Window: +/- 3 Weeks

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc). Refer to instructions above for location of visit checklists.	NA	NA

Pre-visit	Remind the participant that they need to be fasting for this visit.	NA	NA
At Visit	Collect participant's interim medical history	Interim Medical History	Interim Medical History
At Visit	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	ConMeds	Concomitant Medication
At Visit	Conduct a directed/limited physical exam	PE Source	Physical Exam
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Conduct an OGTT	Local OGTT Source	Specimen Collection
At Visit	**Local** lab collection: 1. CBC with differential	Lab Results signed and dated by MD	Local Lab Results
At Visit	**Central** lab collection: 1. Chemistries 2. HbA1c 3. Mechanistic Assessments a. PBMC/Plasma b. Mechanistic Serum	Signed and dated printout of specimen collection form	Specimen Collection
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.60 Month 67 and 68 Interim Phone Contact (through study end)*

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During	Ask the subject regarding the presence or absence of	Phone	Phone

the Call	blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue, and irritability.	Contact	Contact
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

**A phone contact assessment will occur through study end for every month that does not have a random glucose or scheduled visit.*

*5.61 Month 69 Interim Phone Contact (every 3 months through study end**):*

Window: +/- 2 weeks

Time Point	Description of Procedure	Source Document	eCRFs
During the Call	Ask if the participant had any changes in health since last visit.	Phone Contact	Phone Contact
During the Call	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	Phone Contact	Concomitant Medication
During the Call	Ask the subject regarding the presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss, increased hunger, fatigue and irritability.	Phone Contact	Phone Contact
During the Call	Schedule random glucose sample collection.	NA	NA
Post Call	**Central** lab collection: 1. Random Glucose* *Note: If specimen is collected at a lab other than the site, specimen should be sent to the site first, and should then be shipped to the Beta Cell/Biochemistry Core lab.*	Signed and dated printout of specimen collection form	Specimen Collection
Post Call	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Call	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Call	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Call	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

** Participants with symptoms or random glucose >200mg/dl will undergo fasting glucose or OGTT evaluation.*

***The phone contact assessment with Random Glucose should be repeated every 6 months (alternating every 3 months with visit schedule) until end of study.*

5.62 Visit 28 (Month 72-End of Study):*

Window: +/- 3 Weeks

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc). Refer to instructions above for location of visit checklists.	NA	NA
Pre-visit	Remind the participant that they need to be fasting for this visit.	NA	NA
At Visit	Collect participant's interim medical history	Interim Medical History	Interim Medical History
At Visit	Ask the participant about what medications they are currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	ConMeds	Concomitant Medication
At Visit	Conduct a directed/limited physical exam	PE Source	Physical Exam
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Conduct an OGTT	Local OGTT Source	Specimen Collection
At Visit	**Local** lab collection: 1. CBC with differential	Lab Results signed and dated by MD	Local Lab Results
At Visit	**Central** lab collection: 1. Chemistries 2. Liver Function 3. HbA1c 4. Mechanistic Assessments a. Mechanistic Serum	Signed and dated printout of specimen collection form	Specimen Collection
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

**The assessments at month 72 will be repeated every 6 months until end of study.*

5.63 Description of Study Procedures

5.63.1 PPD Test (Screening Visit)

Administration of PPD Test

a. Swab the injection site with an alcohol pad.
b. Administer by injecting a 0.1 mL volume containing 5 tuberculin units PPD into the top layers of skin (intradermally), immediately under the surface of the skin) of the forearm. The turberculin PPD is injected just beneath the surface of the skin. *(Note: Away from veins is recommended.)*
c. A discrete, pale elevation of the skin (a wheat) 6 to 10 mm in diameter should be produced when the injection is done correctly.

Results of PPD

a. The results of the PPD test need to be read within 48-72 hours of administering the test.
b. The test must be read by a trained nurse or physician (either at the study site or at a site more convenient for the participant).
c. The test results should be filed in the participant's source documents.

5.63.2 Pregnancy Monitoring (Screening. Baseline. Visits 16-End of Study)

Females:

Urine pregnancy tests are required for all females with childbearing potential. The test results and method of birth control (including abstinence) should be noted on the source document.

Males:

Method of birth control used with their partners should be noted on the source document. If participant is not sexually active abstinence should be noted for birth control method.

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

Step 1. Contact the TNCC and notify them of the positive pregnancy test.

Step 2. Conduct a confirmatory pregnancy test. (Note: **DO NOT** administer study drug or conduct an OGTT if the participant is confirmed pregnant).

Step 3. Ask the participant if they would be willing to be followed on the study to record information about their pregnancy outcome.

a. If the participant does not want to be followed, withdraws consent, or becomes lost to follow up complete the "Change in Status" form If the participant agrees to be followed,
    i. At the end of the pregnancy, document the pregnancy outcome on the "Pregnancy Outcome" PRN e-CRF.
    ii. Complete study visits as per the study schedule but **DO NOT** administer any further doses of study drug and **DO NOT** conduct any further MMTT's.

Step 4. Place a note to file in the participant binder documenting the conversation and the outcome (i.e. participant agrees to be followed per study, participant does not agree to be followed per study, etc.).

Step 5. Complete the "Pregnancy Confirmation" e-CRF PRN form.

Step 6. Fulfill any local reporting requirements (IRB, GCRC, etc.).

5.63.3 Study Drug Administration (Baseline through Visit 13)

Teplizumab or saline will be given by IV infusion over 14 days in a research or hospital setting. All infusions must take place in a facility that has resuscitation capabilities. It is the responsibility of the site PI to ensure all on site study personnel conducting infusions are trained and certified to safely complete this study procedure and evaluation of corresponding tests.

- Teplizumab or saline must be given as an IV infusion over a minimum of 30 minutes.
- Once the study drug has been infused over a minimum of 30 minutes, the administration set should be flushed at the same constant rate as the infusion with a volume of 0.9% Sodium Chloride Injection equivalent to the priming volume of the IV administration set.

- Chemistries, liver function studies, CBC with differential, and INR studies will be run locally and evaluated before drug is administered on each day that these studies are drawn.

- The infusions are given at baseline through day 13.

- Dosing will not be done in subjects with a febrile illness within the previous 24 hours. These subjects will be rescheduled for another day within a five day window.

- Prophylactic Medications: Ibuprofen and antihistamine will be administered prophylactically prior to teplizumab/placebo infusion on the first 5 days of treatment. Further dosing of Ibuprofen, antihistamines, and/or acetaminophen can be used as needed for fever, malaise, headache, arthralgia, or rash.

5.63.3.1 Dosing Calculation

The subject's BSA will be calculated by the pharmacist using the Mosteller formula. (Please see the Pharmacy Manual section 5.5 for correct formula calculation and additional instructions for study drug dosing.)

For dosing purposes the participant's BSA should be rounded up to the nearest tenth place regardless of the number in the hundredth position For example, if the BSA is 1.61, it will be rounded up to 1.7 and if the BSA is 1.67, it will also be rounded up to 1.7. The dose should be rounded to the nearest whole number. For example if the participant's BSA is 1.722, on Day 0 the participant would receive 87µg.

5.64 End of Study Participation

5.64.1 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.

5.64.2 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).

5.64.3 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."

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

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

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

5.65 Onset of Diabetes

Criteria for diabetes onset are, as defined by the American Diabetes Association (ADA), based on glucose testing, or the presence of unequivocal hyperglycemia with acute metabolic decompensation (diabetic ketoacidosis). One of the following criteria must be met on two occasions as soon as possible but no less than one day apart for diabetes to be defined:

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

OR

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

OR

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

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

If a participant has an OGTT that indicates diabetes (clinical alert), the site should invite the participant for a repeat OGTT within 60 days. In order to make a diagnosis of diabetes, each of two consecutive OGTTs must meet diabetes criteria. Thus, if the second OGTT does not confirm the diagnosis, the participant will continue to be followed in the Anti-CD3 Prevention Study and will be asked to return for the next follow-up visit. At that time, the OGTT will be repeated and, if indicative of diabetes, will need to be performed a second time to confirm the diagnosis.

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

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

AND/OR

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

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

1. Complete the “Change in Study Status” e-CRF PRN in the online electronic data capture system and indicate that the subject has developed Type 1 Diabetes and is inactive.
    a. The “Date change in status became effective” should reflect the date the participant was diagnosed with type 1 diabetes.
    b. Proceed to section B, enter a date of withdrawal and indicate the primary reason for withdrawal (development of T1D).
2. If the subject is within the Study Drug Administration Phase of the study (Visits # 0, Baseline through Visit # 13, Month 12), the subject will no longer be able to continue with study drug administration. Please complete the TN10 Change in Study Drug eCRF and indicate the study drug has been discontinued.
    a. The reason should be “development of T1D”.
3. Complete the TN10 “Diabetes Onset Form” in the online electronic data capture system and indicate that the participant has developed diabetes.

The date of diagnosis will be defined as follows:

1. If the participant was symptomatic at diagnosis, the date of diagnosis will be the date of the **first** OGTT.

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

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

a) It is *strongly preferred* that at least one of the required diagnostic OGTTs be performed at a TrialNet Center or Affiliate and that the samples for plasma glucose, C-peptide and insulin levels be sent to the TrialNet Beta-Cell Function Laboratory.

b) For testing that cannot be done at a TrialNet Center or Affiliate, it is *strongly preferred* that the samples be collected and sent to the TrialNet Beta-Cell Function Laboratory for plasma glucose levels rather than relying on test results from the local (non-TrialNet) lab.

c) The judgment about whether to perform an OGTT when there is concern that it will affect the participant's safety should be made by the Center Director or Affiliate physician. [NOTE: All participants with fasting glucose levels ≥ 126 mg/dL (7.0 mmol/L) should be evaluated for the presence of symptoms and ketones prior to performing the OGTT.]

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

Scenario 1:

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

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

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

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

Scenario 2:

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

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

Scenario 3:

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

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

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

Scenario 4:

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

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

Scenario 5:

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

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

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

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

Scheduling Confirmatory OGTTs:

When a participant has an OGTT result that indicates diabetes (clinical alert), the site will receive an email notification from the TNCC and lab stating "Repeat OGTT requested. Follow your study procedures for the next action to take or contact your TNCC Clinical Research Administrator." The site should contact the participant to schedule a confirmatory OGTT as soon as possible and no more than 60 days after the first clinical alert OGTT was collected.

A request to repeat the OGTT should not be interpreted as a diagnosis of diabetes when asking subjects to schedule a confirmatory test. It is important to explain to subjects that these findings need to be confirmed before making a diagnosis of diabetes. In addition to temporary metabolic

fluctuations due to illness or stress, there may be other reasons why an OGTT may need to be repeated (e.g. laboratory error, degradation of sample, shipping problems, etc.).

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

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

5.66 Death

All deaths are considered serious adverse events and should be reported within 24 hours of notification, as this is an unexpected event for participants in the Oral Insulin Study. Site coordinators 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.

5.67 Missed Visits/Visits Occurring Outside Window

5.67.1 Missed Visit

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

1. For that visit time point, under "Tracking" select "Not Done" for all forms and indicate the reason the visit was not completed within the allowable window.
2. Document the reason for the missed visit in the source.

5.67.2 Visit Occurs Outside of Allowed Window

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

1. Complete the visit e-CRF's using additional study forms (PRN forms).
2. For that visit time point, under "Tracking" select "Not Done" for all forms and indicate the reason the visit was not completed within the allowable window.
3. Complete one Protocol Deviation form indicating that the visit and samples were collected outside of the allowable visit window.

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.

6.1.3 Post-Infusion Transfer Procedures:

If the participant is just being transferred back from the infusion site to the enrolling site for follow-up the following procedures should occur:

Step 1. During the last 2-3 days of the participant's treatment:

i. The infusion site **MUST**:

1. Review all data and e-CRF's; complete and enter all missing visit data and attempt to reconcile any missing or outstanding tests results/adverse events/source documents.
2. Contact the originating site to notify them of the date when infusions will be completed.
3. Inform the originating site to contact the participant to schedule their first post-infusion follow-up visit.
4. Make note of the follow-up visit date.

ii. The originating site **MUST**:

1. Schedule the participant for their first post-infusion follow-up visit and explain the follow-up process and consent form, if not previously signed, to the participant.

Step 2. Once all data has been entered/reconciled, and the subject has been given a date for the first post-infusion follow-up visit at the originating site, on the day before the subject's scheduled visit, the infusion site must navigate to the PRN form "Participant Site Transfer" and transfer the subject back to their original site and select "Participant completed infusions; transferring back to primary site" as the reason for the transfer. See section 9.6 for instructions on how to access PRN forms.

Step 3. The infusion site will notify the originating site when the participant has been transferred in the online system.

Step 4. The originating site must bring the subject in to review the follow-up consent (if applicable) and discuss any final questions or concerns the subject/parent may have regarding the follow-up period prior to the subject/parent signing the consent forms.

Step 5. Proceed with conducting the follow-up visits as indicated per protocol and completing all applicable all e-CRF's.

6.2 Remote Participant Visits

6.2.1 Conducting a Study Visit at an Unapproved Site for an Interventional Study

Sites should not transfer participants to a site that is not approved for the study. No study procedures (other than remote specimen collection procedures) can be performed at an unapproved site. A study visit includes any procedure other than a specimen collection.

6.2.2 Collecting Specimens at an Unapproved Site

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

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

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

Procedures:

Step 1. The unapproved site needs to be currently approved by TrialNet for at least one TrialNet protocol. This approval must be on file at the TNCC OR be a lab vendor.

Step 2. The unapproved site only conducts procedures that they already conduct under the approval of another TrialNet protocol or for which they have appropriate training/resources already in place.

Step 3. The unapproved site **will not use** any of the online specimen collection forms for the visit.

a. The unapproved site should use its own source documents for the visit.

Step 4. The unapproved site **will not use** the online Specimen Management System (SMS).

Step 5. The site may choose to use its own supplies to collect specimens or may request a study kit per its Clinical Center's current procedure.

Step 6. Upon completion of the study visit, the unapproved site will send *all* samples collected and source documents via FedEx to the enrolling site immediately.

Step 7. The enrolling site will enter the visit online using online specimen collection forms, etc and use the online specimen shipment system to ship specimens to the proper lab.

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

7. Informed Consent

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

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

7.1 Required Elements of Informed Consent

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

1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

2) A description of any reasonably foreseeable risks or discomforts to the subject.

3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

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

1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

3) Any additional costs to the subject that may result from participation in the research.

4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

6) The approximate number of subjects involved in the study.

Applies only to protocols approved after March 12, 2012:

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

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

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

7.1.1 Assent of Children

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

7.2 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

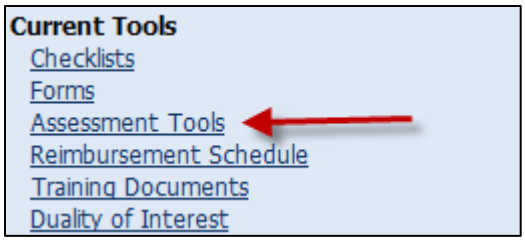
7.2.2 Documentation of the Informed Consent Process

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 TN10 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.

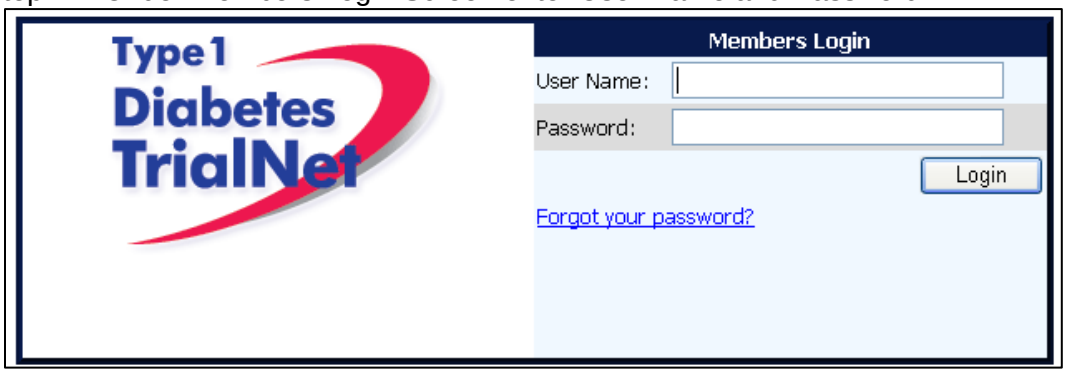
9. Online Data Capture System

9.1 Overview and Basic Functionality

9.1.1 Login/Navigate to the TN10 Protocol Manager Area

Step 1. Procedure to login and navigate to the TN10 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.

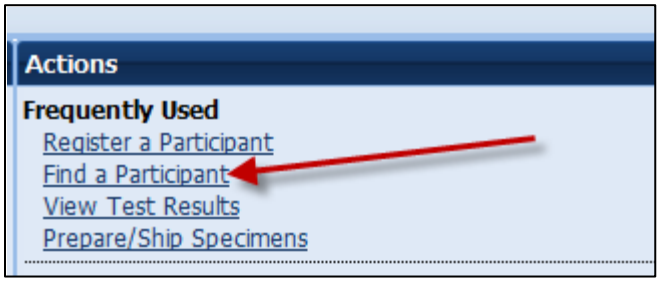


Step 3. Navigate to the “Protocols” portlet. Under TN10, select “Protocol.”

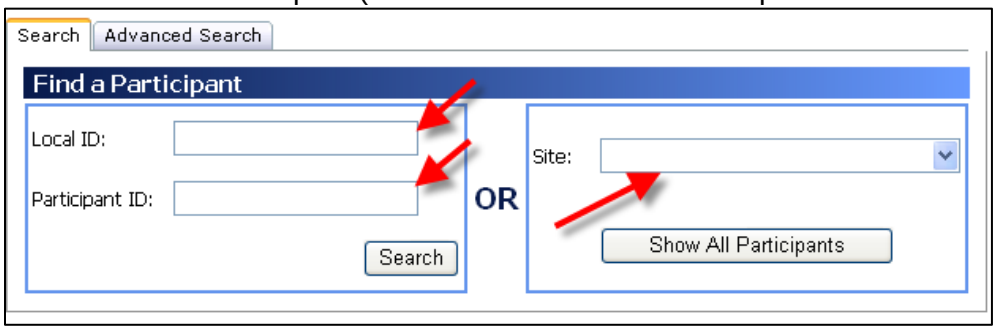
9.1.2 Finding a Participant

Note: This procedure will be done for every visit.

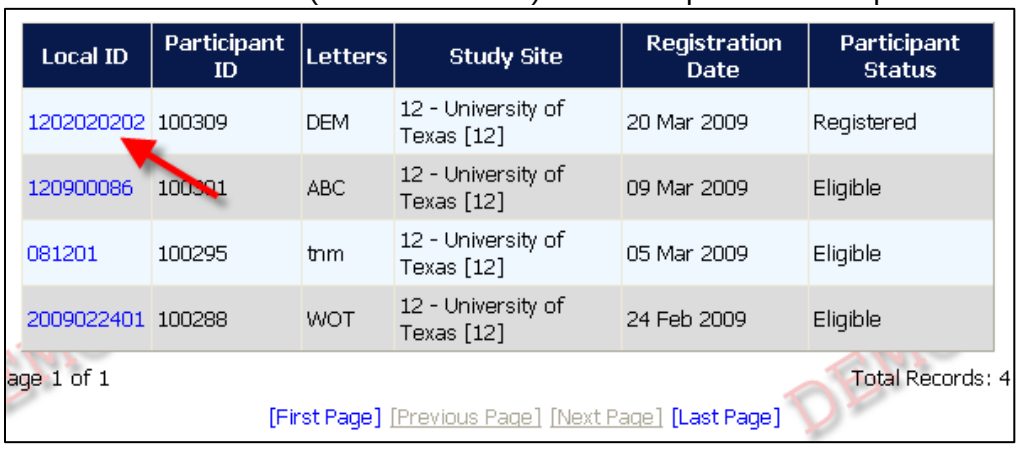
Step 4. Procedure to find participant: Once in TN10 Protocol, navigate to the "Actions" portlet and select "Find Participant."



Step 5. Search for Participant (Enter either Local ID or Participant ID or search by site).



Step 6. 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

age 1 of 1 Total Records: 4

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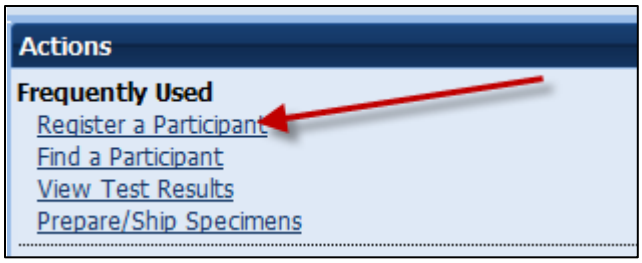
9.1.3 Registering a Participant

Step 1. Log into TrialNet Members Website and navigate to the Protocols portlet. Select the "Protocol" link under TN10 – Anti-CD3 Prevention (see section 9.1.1 for detailed instructions.)

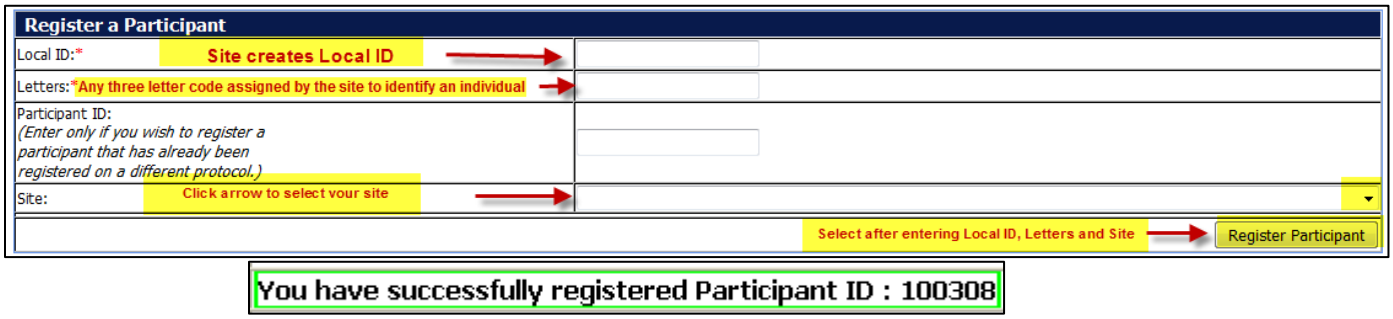
Step 2. Once in TN10 Home Page, navigate to the Actions portlet and select "Register Participant."



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

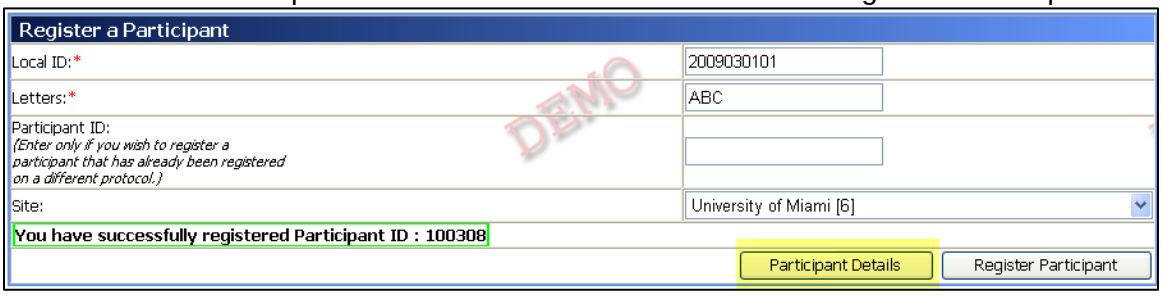
a. Local ID: The site can enter the desired local ID for the participant. This can include numbers and letters.
b. Letters: Enter three letters.
c. Participant ID: ID should remain the same for interventional studies
Note: PID should be skipped if first time participant on TrialNet study.
d. Site: Select applicable site.

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



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.

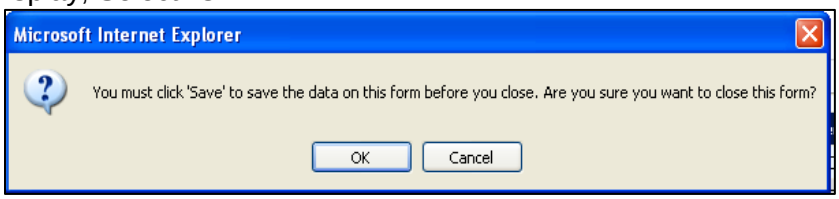


9.1.4 Save and Close e-CRFs

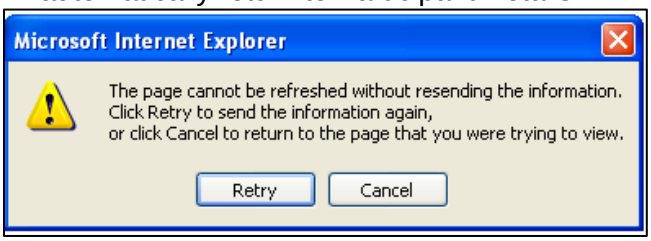
Note: This procedure will be the same after each e-CRF is completed.

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

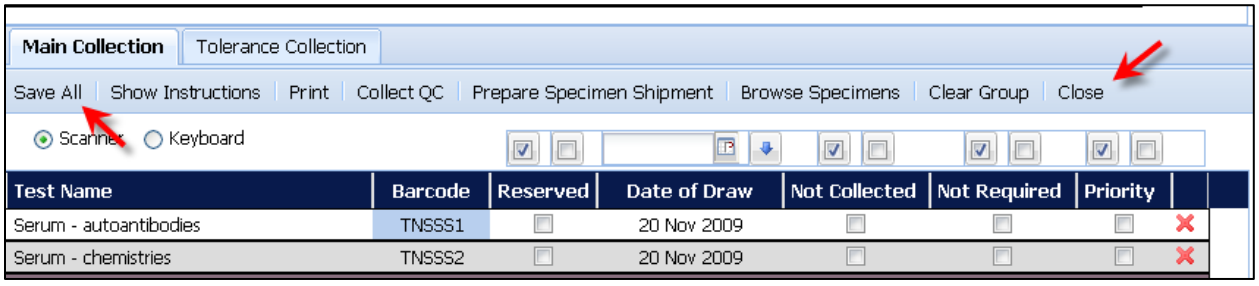


9.1.5 Save and Close Specimen Collection Forms

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

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

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

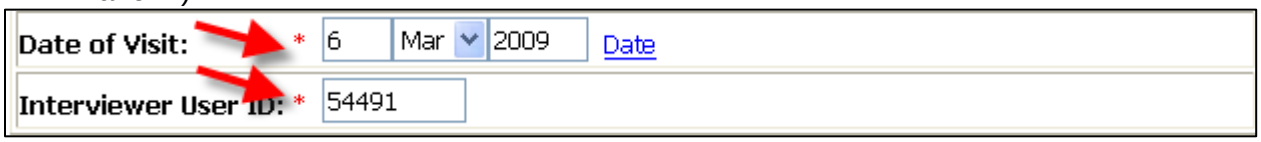


Please review the TrialNet Specimen Management System User Manual for potential error messages you may receive when attempting to save a collection form and additional information regarding collection forms.

9.1.6 Form Required Fields

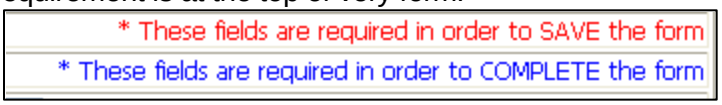
There are two kinds of required fields on every form:

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:

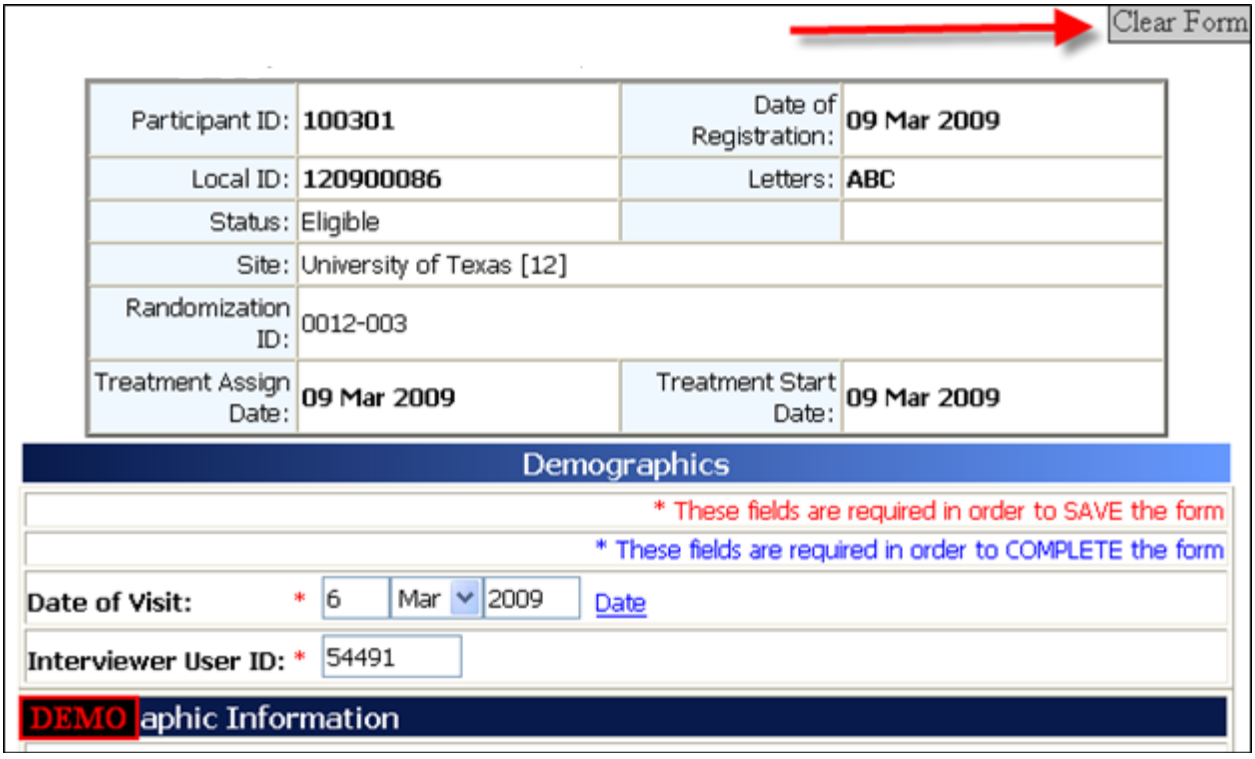


9.1.7 Clear ALL Data from a Form

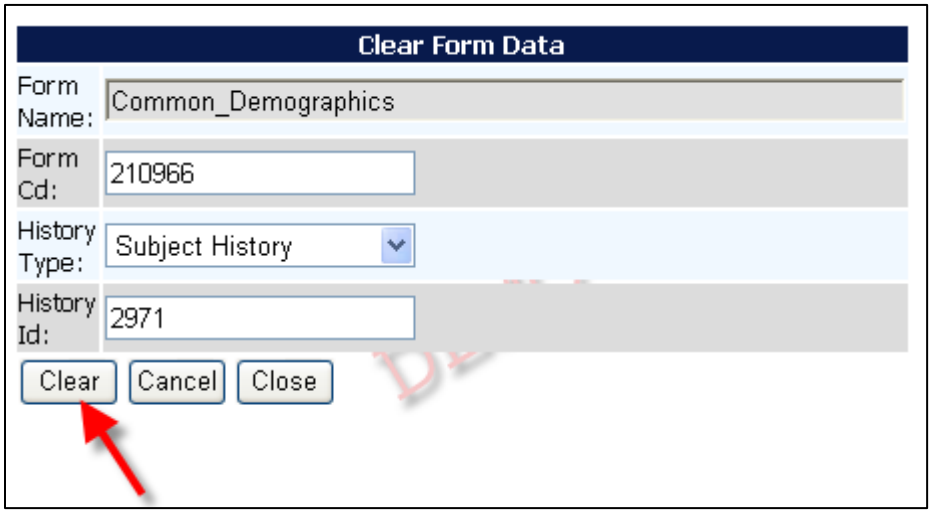
If you find you have mistakenly entered wrong data on a form, you can clear all data on the form as long as you are the person who entered the data on the form (determined based on the Interviewer user ID entered in the form).

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

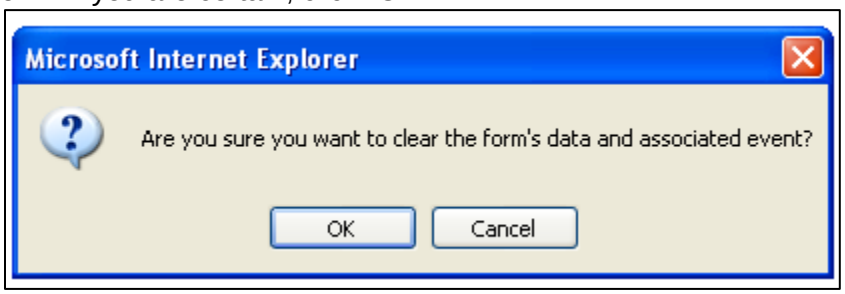
Step 2. Click on the button entitled “Clear Form” in the upper right hand corner of the screen.



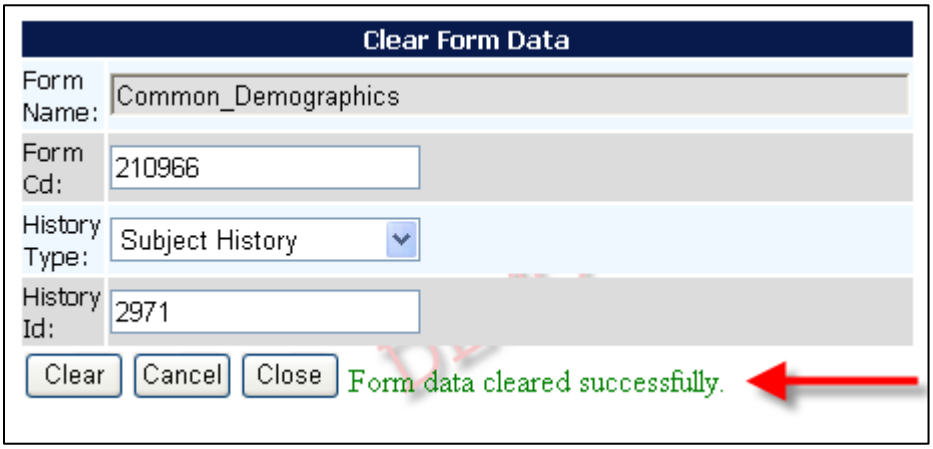
Step 3. The page will navigate to a description of the form you are about the clear (Clear Form Data box). If you are certain you wish to clear out all data on the form, click the button “Clear.”



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.

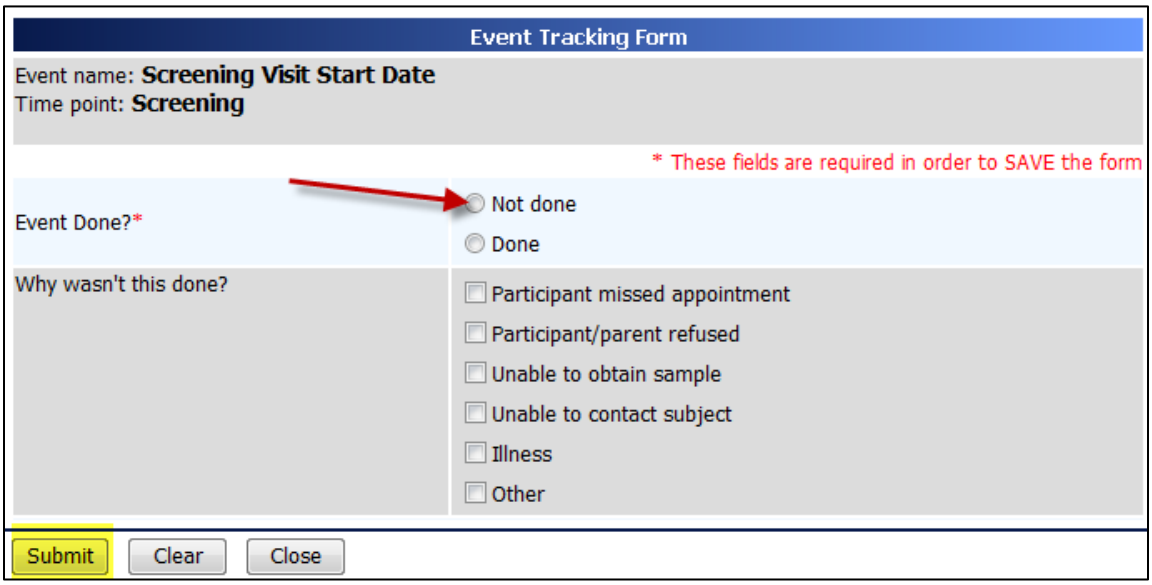
9.1.8 Clear ALL Data from a Collection Form

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	Target Date	Due Date	Last Modified Date	Event Status
Screening	Screening Informed Consent Verification		06 Sep 2012	06 Sep 2012	08 Oct 2012	Complete
	Screening Medical History		06 Sep 2012	06 Sep 2012	08 Oct 2012	Complete
	Physical Exam		06 Sep 2012	06 Sep 2012	08 Oct 2012	Complete
	Pregnancy Monitoring		06 Sep 2012	06 Sep 2012	08 Oct 2012	Complete

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



- 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

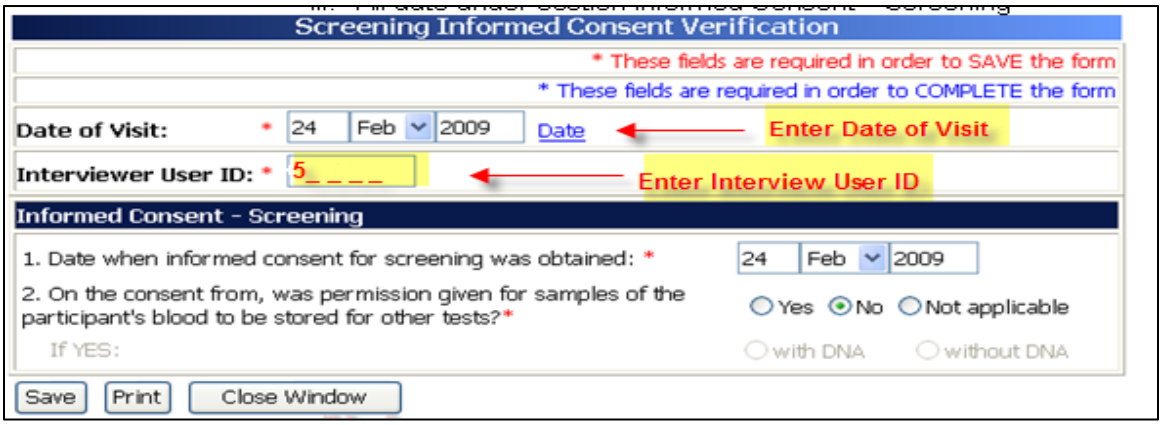
9.3.1 Data Entry for All Visit Forms

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.

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

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



Step 4. Complete all sections of the form

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)

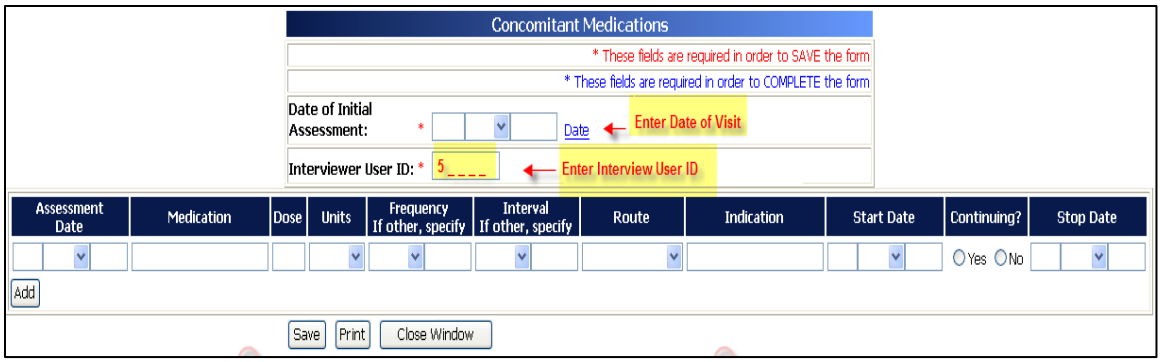
9.3.2 Concomitant Medications

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.

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.



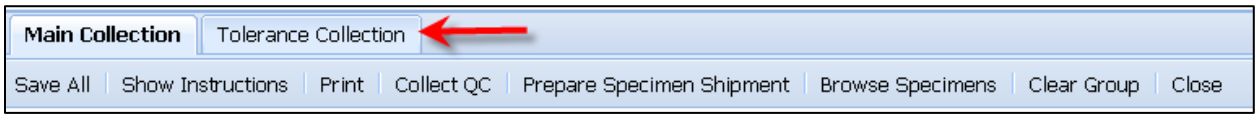
9.3.3 Specimen Collection Form: Main Collections

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 include OGTTs, IVGTTs, and MMTTs.

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

9.3.4 Specimen Collection Form: Tolerance Collections

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



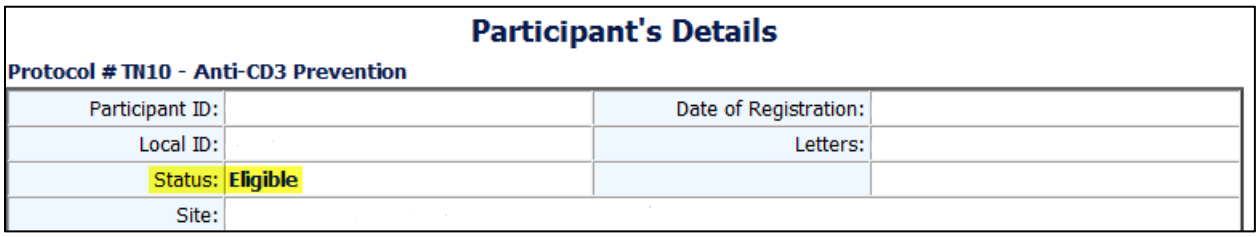
After completing the Main Collections navigate to the "Tolerance Collection" by selecting the "Tolerance Collection" tab.

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

9.3.5 Baseline Eligibility Form

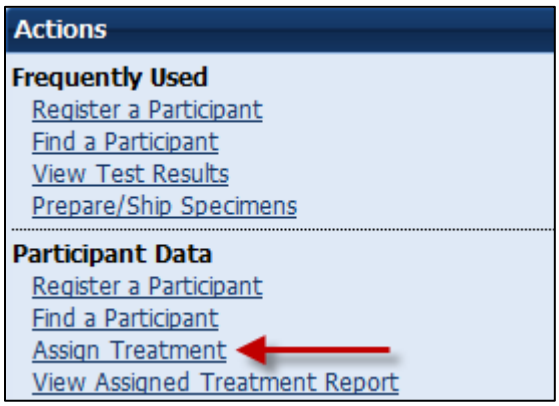
Note: This form will determine the status of the participant's eligibility in the study.

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



9.3.6 Participant Treatment Assignment

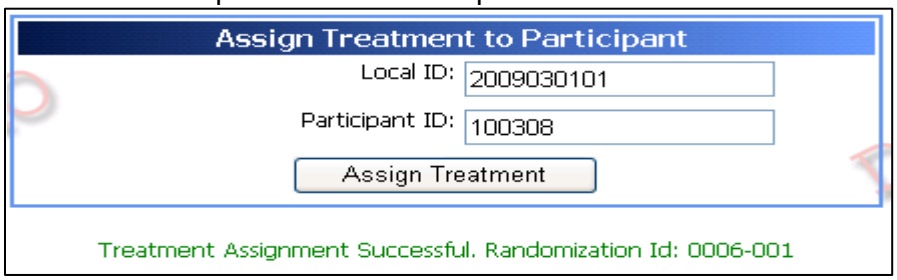
Step 1. The ***Eligibility form must be complete*** and the subject must be eligible prior to assigning treatment to the subject. Under the Actions portlet on the main protocol page select "Assign Treatment"



Step 2. A box will open titled Assign Treatment to Participant; enter both the Local ID and Participant ID.

Step 3. Select Assign Treatment.

Step 4. A message will reflect Treatment Assignment Successful and the Randomization number will be provided. For example:



Note: Each randomization number will only be assigned once.

Step 5. Make note of the randomization number in the source documents.

Step 6. Contact the local site pharmacist (assigned on this study) and provide the pharmacist the randomization number.

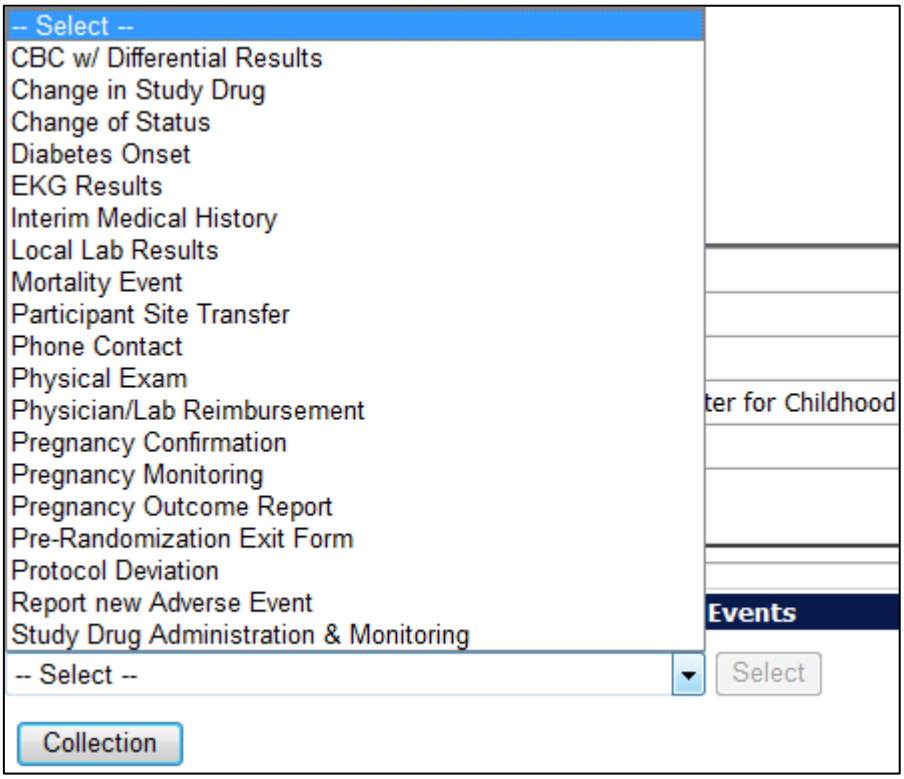
9.4 PRN Forms

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

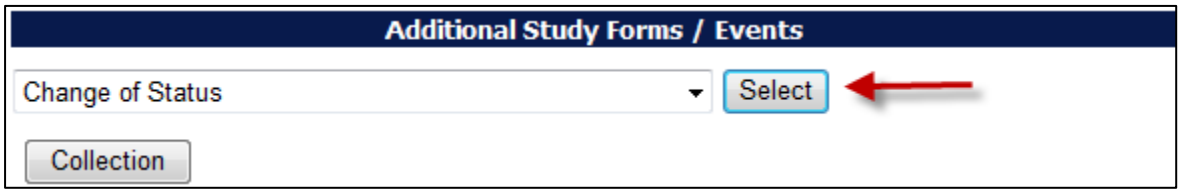
9.4.1 Open a New Additional Study Form/Event (PRN Form)

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.

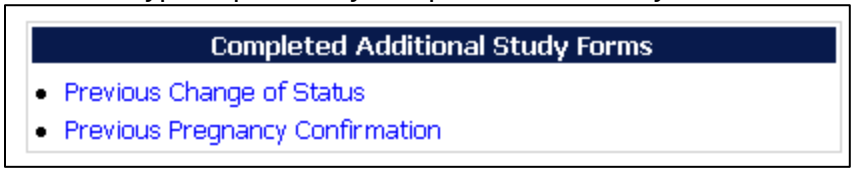


Step 4. A new window will open with the selected form.

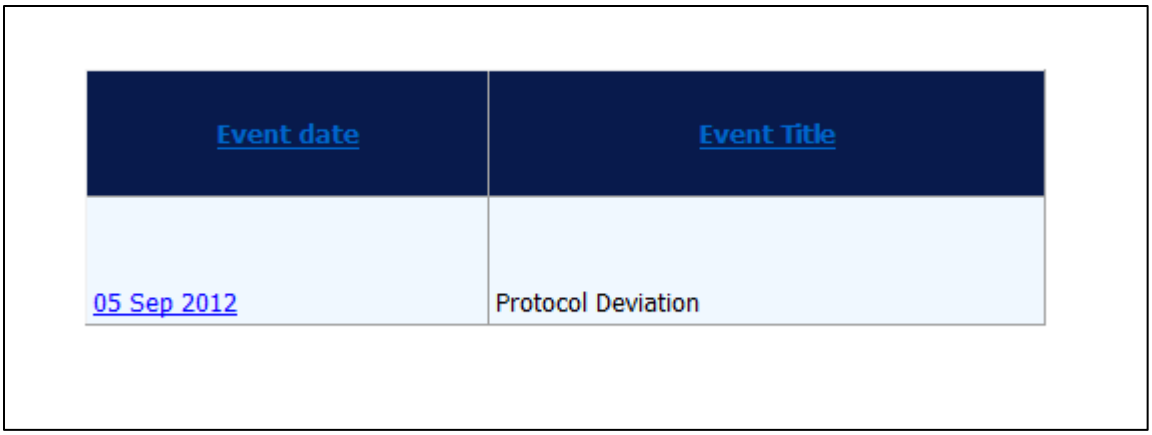
9.4.2 Open a Previously Completed Additional Study Form/Event (PRN Form)

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.



Event date	Event Title
05 Sep 2012	Protocol Deviation

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 whether or not associated with the treatment and 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 must be reported on the appropriate adverse event form as described below. The investigator should treat participants with adverse events appropriately and observe them at suitable intervals until the events resolve or stabilize.

For this trial, an adverse event associated with the treatment or study procedures that suggests a significant hazard, contraindication, side effect or precaution (as described below) is to be reported as a **serious adverse event (SAE).** A serious adverse event or reaction is any untoward medical occurrence that:

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

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

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

Data Descriptions:

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

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

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

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

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

Using the CTCAE:
TrilaNet provides several resources for the proper use of CTCAE codes for adverse event reporting. Because the NCI has developed and maintained the CTCAE classification, the recommended educational materials are from the NCI. Each person entering data in the AE system should be given a copy of a small spiral-bound booklet titled "Common Terminology Criteria for Adverse Events (CTCAE), version 3.0." [NIH Publication No. 03-5410.] This booklet contains the entire CTCAE, with descriptions of each event and grade. The CTCAE version 3.0 is included in this manual as Appendix C. (For the location of all appendices please reference section 11.1.3)

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.

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

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

The NCI also posts an Index to the CTCAE at:
http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_index.pdf

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

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

10.2 Reporting Timeline

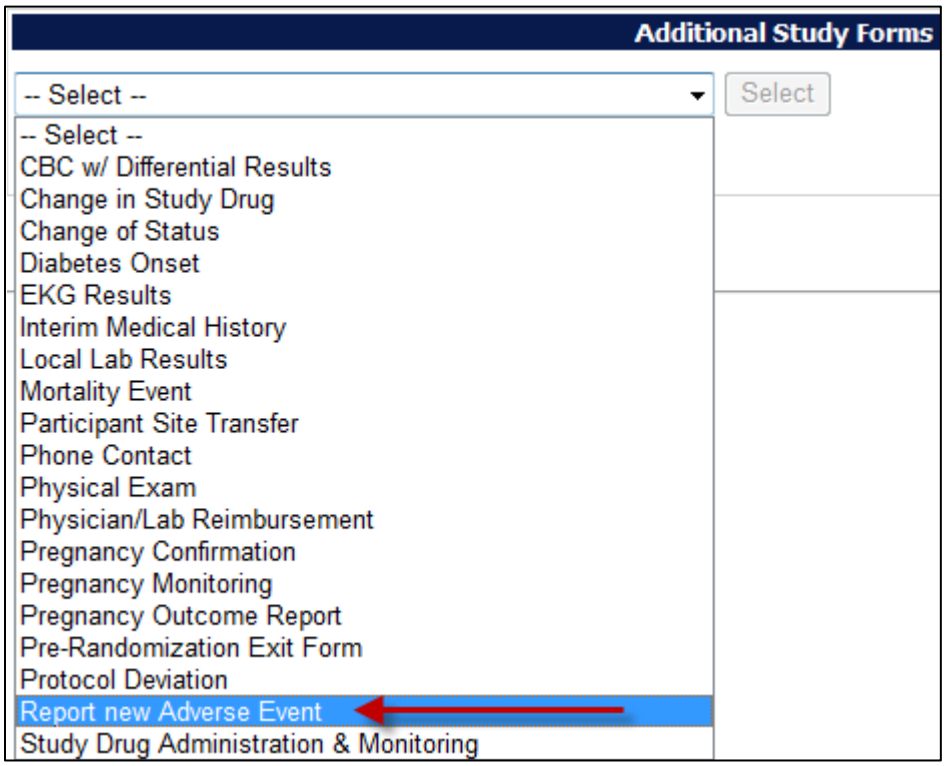
Follow the timelines below for the reporting of adverse events:

- Within **24 hours** (of learning of the event), investigators must report any Serious Adverse Event (SAE) that:
  Is considered life-threatening/disabling or results in death of subject
  -OR-
  Is Unexpected/Unanticipated
- Investigators must report all other SAEs within **5 working days** (of learning of the event).
- All other (suspected) AEs must be reported to the TNCC within **20 working days** of the notification of the event or of the site becoming aware of the event.

10.3 Directions for Reporting AE's / System Description

10.3.1 Navigating to the Adverse Event Form

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

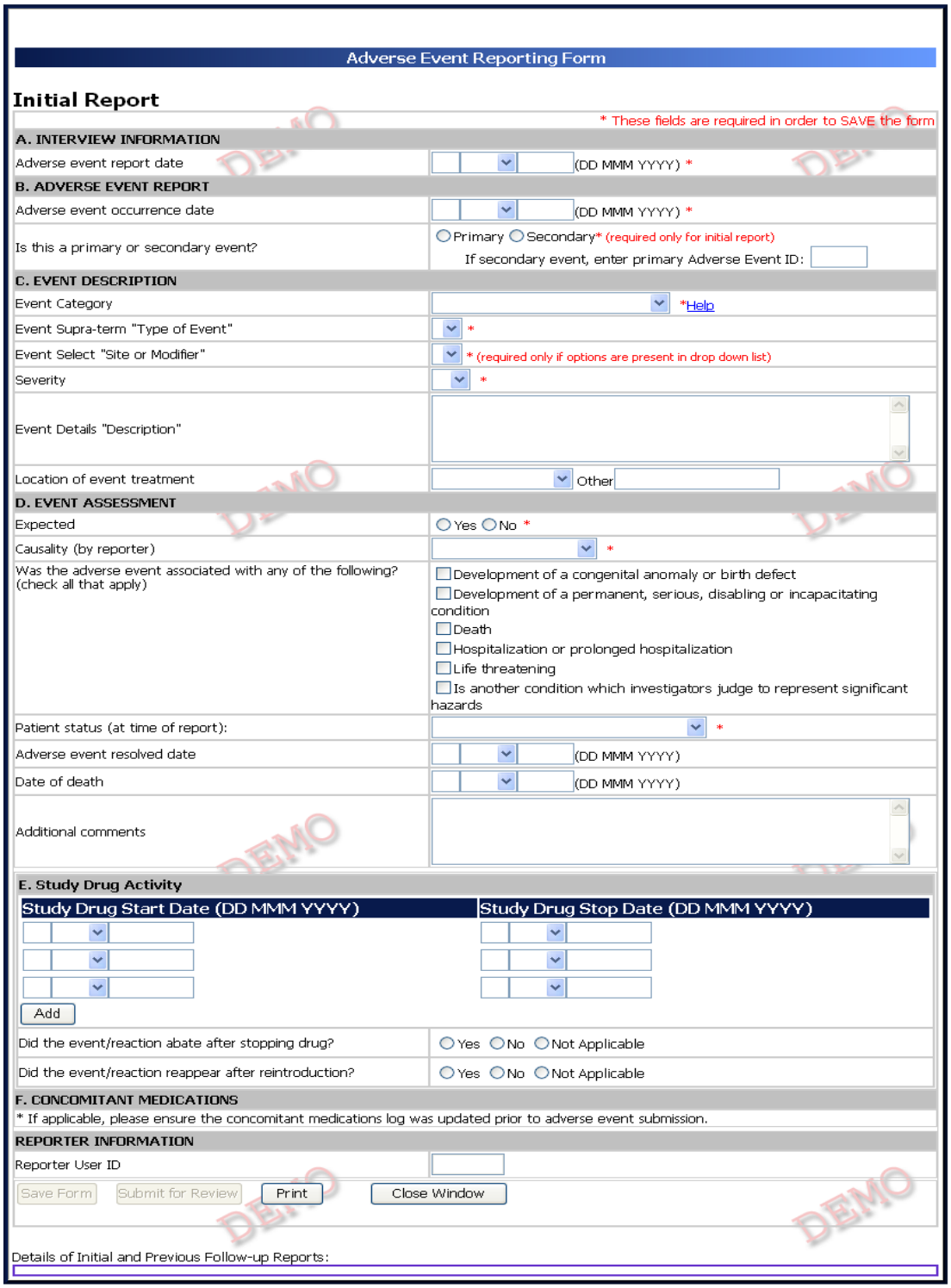


10.3.2 Reporting an Adverse Event

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. NOTE: This option does not submit the AE. To submit an Adverse Event you must select the "submit for review" option. "Save draft" allows you to re-open the form later and submit the event at a later time.
b. To submit the report, click on "Submit for review."
   i. NOTE: 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

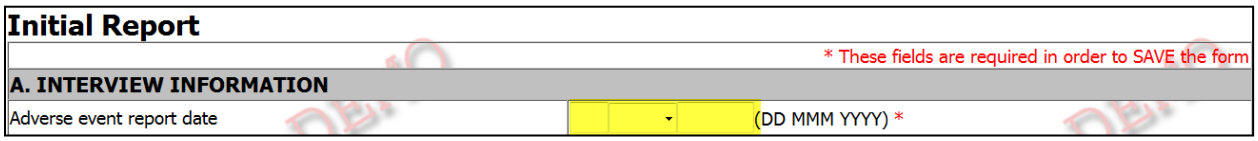
Save Form Submit for Review Print Close Window

Details of Initial and Previous Follow-up Reports:

Adverse Event Reporting – Description of each field:

Section A. Interview Information:

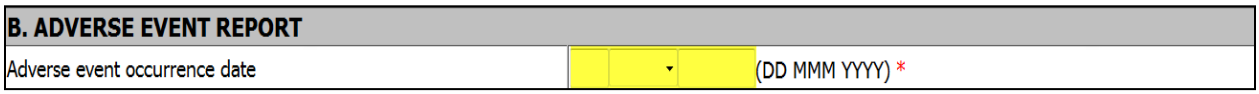
- Adverse event report date (image 1): This section refers to the date the event was first learned. Note: This is not the date the AE Reporting Form is completed.



Section B. Adverse Event Report (Image 2)

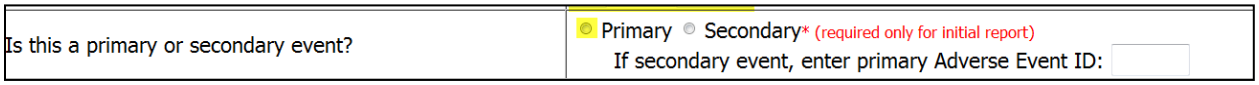
- *Adverse Event Occurrence date*: This refers to the date on which the adverse event began.

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



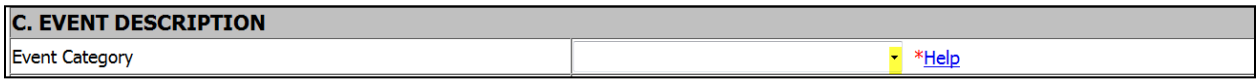
- Is this a primary or secondary event?(Image 3):
  - A **primary** AE is the main event.
  - A **secondary** AE is not a worsening or change in severity of the primary event, but it is an AE caused by or related to the primary event. *If reporting a secondary event, the AEID of the related primary AE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

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



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.



- *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 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. Note: This does not determine if event is a serious adverse event.

Severity	*

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

Note: Do not indicate PHI including gender of participant.

For Example:

Not Acceptable: *"He developed a rash."*
Acceptable: *"The **subject** developed a rash"*

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

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

Location of event treatment	Other

Section D: Event Assessment:

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

D. EVENT ASSESSMENT	
Expected	Yes No *

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

Causality (by reporter)	*

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

Was the adverse event associated with any of the following? (check all that apply)	☐ 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. Study Drug Activity:

- *Study Drug Start Date / Study Drug Stop Date*: Enter the date administration was started and the date stopped (for some studies best estimate will suffice). This section is completed if applicable. This section should be completed if AE/SAE occurred while on study treatment.

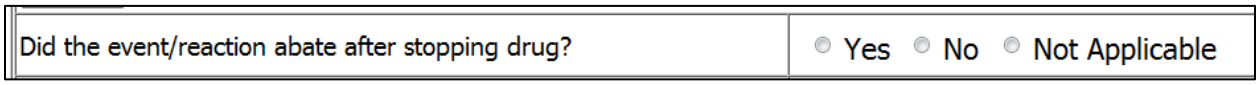
Note: Further clarification in section 10.3.3: Section E. Study Drug Activity: Study Drug Stop/Start Date.

E. Study Drug Activity

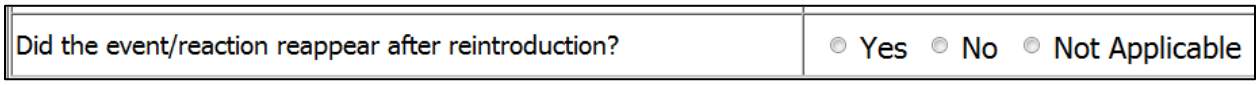
Study Drug Start Date (DD MMM YYYY)	Study Drug Stop Date (DD MMM YYYY)

Add

- Did the Event/Reaction Abate after stopping drug?:
  a. Enter “Yes” if AE being reported resolved after treatment was stopped; or
  b. Enter “No” if AE being reported did NOT resolve after treatment was stopped; or
  c. Enter “Not Applicable” if the study drug was not stopped or if study was never restarted.

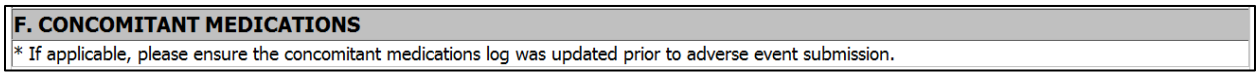


- Did the event/reaction reappear after reintroduction?:
  a. Enter “Yes” if AE being reported reoccurred after treatment was restarted; or
  d. Enter “No” if AE being reported did NOT reoccur after treatment was restarted; or
  e. Enter “Not Applicable” if the study drug was not stopped or if study drug was never restarted.

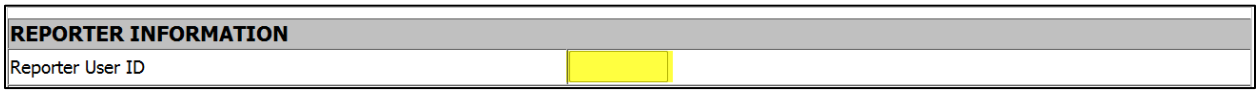


Section F. Concomitant Medication:

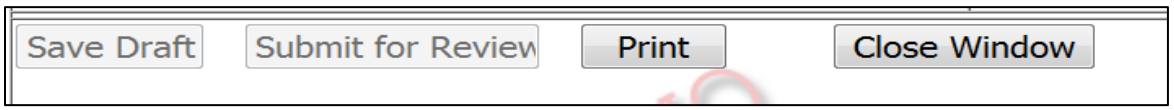
Prior to submitting the adverse event make sure any additional concomitant medications are listed in the concomitant medication running log prior.



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



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

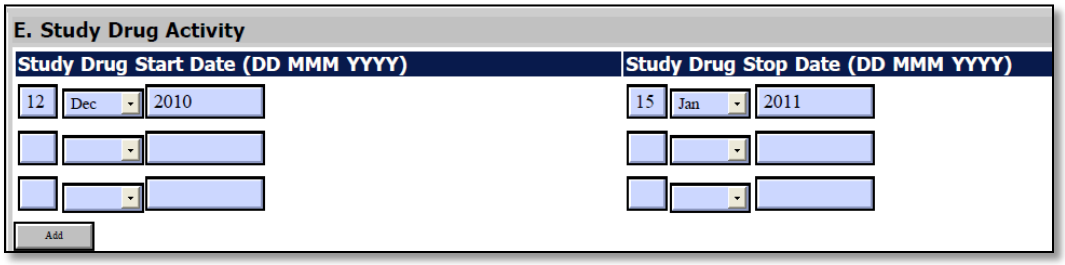


Note: Contact TNCC CRA if there are any additional questions regarding this form

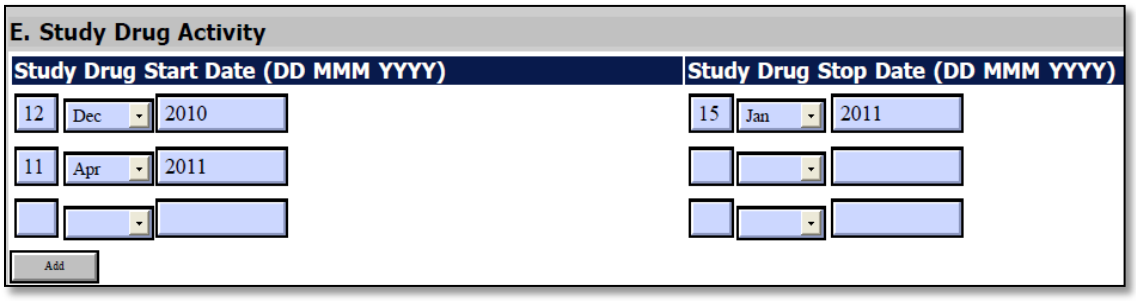
10.3.3 Clarification: Section E. Study Drug Activity: Study Drug Start/Stop Date

Start Date is based on the day the subject received their first study treatment. For instance: Participant 123456 received first study drug on 12/12/2010, the **Start Date** would be that date.

Stop Date is date study treatment is stopped. To clarify further, the **Stop Date** would only be entered if participant did not receive one of their number of study treatments expected per protocol. For instance: Participant 123456 missed Visit 3 for any reason, but received their Visit 2 study treatment (date 1/15/2011), the **Stop Date** is the date of the last study treatment was received.



If at a later time, in the study, another adverse event needs to be reported and the participant has since resumed their study treatment, the **Start Date** would be the visit date when the participant resumed study treatment. For instance: Participant 123456 missed visit 3 and visit 4 for any reason, but resumed treatment at visit 5 (date 4/11/2011) then the next **Start Date** entered would be 4/11/2011.



**Note: If study treatment is not given due to an AE/SAE, please be certain to note that in the description of the AE form.*

10.4 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.

10.5 Reporting to the FDA

In addition to the reporting requirements for the TrialNet network (as described above) the FDA requires reporting of adverse events **only** when they are determined (based on medical monitor, investigator and/or sponsor review) 1) serious, 2) unexpected, and 3) a result of a Suspected adverse reaction to the study drug (21CFR312.32 (c)(i)(A)-(B)). If the event does not satisfy all three of these criteria, it should not be reported to the FDA. These adverse events must be submitted within 15 days.

The sponsor must also report expeditiously (within 7-15 calendar days) any findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug (21 CFR 312.32(c)(1)(ii) and (iii)).

Finally, the sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure (21CFR 312.32(c)(1)(iv)).

The process for reporting to the FDA is as follows:

3. Site/TNCC completes 3500A MedWatch report (mandatory reporting form).
    a. Link to form: http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM082728.pdf
    b. Instructions for completing form: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/ucm149238.htm
4. Site emails completed 3500A MedWatch report to TNCC CRA and TrialNet Medical Monitor (Brett J. Loechelt, MD; bloechel@cnmc.org)
5. Within 15 calendar days (or 7 calendar days if fatal or life-threatening***** suspected adverse reaction)***** of being notified of the event, the TNCC sends the 3500A MedWatch report to FDA
    a. FDA recommends the sponsor notify FDA by telephone, email or facsimile transmission prior to submitting the MedWatch Report.

***FDA believes that the sponsor is better positioned than the individual investigator to assess the overall safety of the investigational drug because the sponsor has access to serious adverse event reports from multiple study sites and is able to aggregate and analyze these reports. For this reason, investigators must immediately report any serious adverse event to the sponsor, without regard to causality (21 CFR 312.64(b)). However, it is also important for the sponsor to consider the investigator's view when assessing the safety of the drug and determining whether

to report expeditiously to FDA because the investigator is knowledgeable about the human subject (e.g., medical history, concomitant medications), administers the investigational drug, monitors the subject's response to the drug, is aware of the subject's clinical state and thus may be sensitive to distinctions between events due to the underlying disease process versus events that may be drug-related, and may have observed the event.

****The FDA Final Rule on Safety Reporting Requirements for INDs and BA/BE Studies dated September 29, 2010 (21 CFR Parts 312 and 320) defines a "Suspected adverse reaction" (21CFR 312.32(a) as "any adverse event for which there is a reasonable possibility that the drug caused the adverse event". For the purposes of IND safety reporting "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug. The following are examples of types of evidence that would suggest a causal relationship between the drug and the adverse event:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)

- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)

- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Inherent in this definition and in the requirement to report them is the need for the sponsor to evaluate the available evidence and make a judgment about the likelihood that the drug actually caused the adverse event.

*****Under 21 CFR 312.32(c), the sponsor is required to notify FDA and all participating investigators in an IND safety report of potentially serious risks from clinical trials or any other source, as soon as possible, but no later than 15 calendar days after the sponsor receives the safety information and determines that the information qualifies for reporting.

Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and, therefore, must be reported more rapidely to FDA (21CFR 312.32(c)(2)). Any unexpected fatal or life-threatening suspected adverse reaction must be reported to FDA no later than 7 calendar days after the sponsor's initial receipt of the information (21CFR 312.32(c)(2)).

******An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

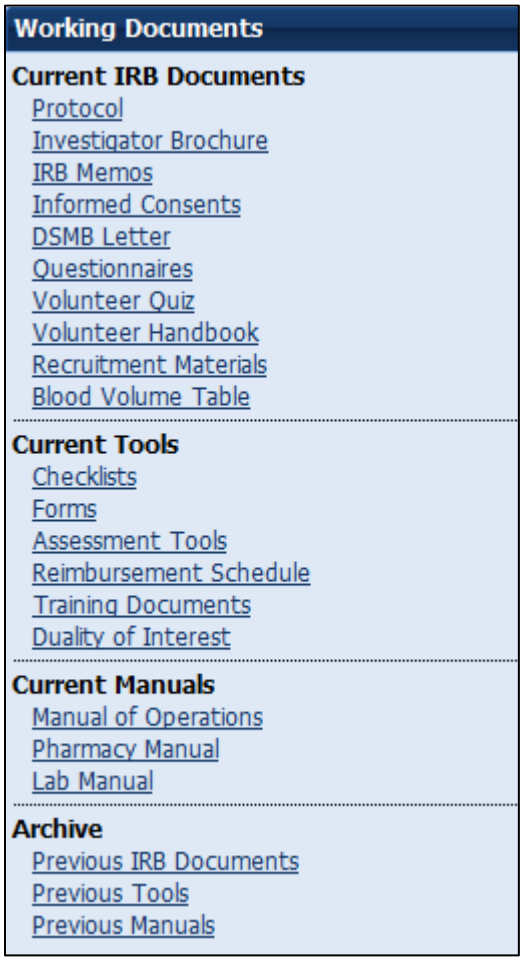
Source: FDA Draft Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies (September 2010).

11. Protocol Manager: Portlets and Tools

From the TN10 – Anti-CD3 Prevention homepage, there are a series of portlets meant to assist/aid sites in the conduct of the study.

11.1 TN10 – Working Documents Portlet

From the TN10 – Anti-CD3 Prevention homepage, the latest protocol related documents, manuals, and other materials to aid sites in the conduct of the study are available in the "Working Documents" portlet.



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. Visit Checklists
2. Forms
    a. Pharmacy Forms

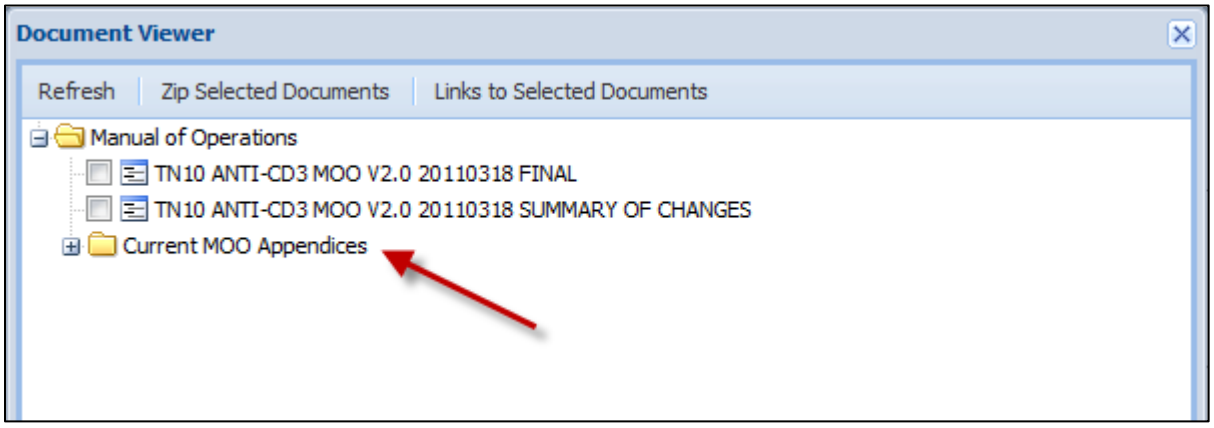
   b. Current Site Forms
   c. Lab-related Forms
3. Assessment Tools
   a. Template source documents
4. Reimbursement Schedule
5. Training Documents
   a. Training Presentations and materials related to the study
   b. Certification Quizzes.

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:
      i. Appendix A Common Definitions
      ii. Appendix B OGTT Instructions
      iii. Appendix C CTCAE Version 3.0
      iv. Appendix D EKG Instructions
2. Pharmacy Manual of Operations
   a. Tracked and clean versions of the current Pharmacy MOO
3. Lab Manual
   a. Current Lab MOO
   b. Protocol specific appendices

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

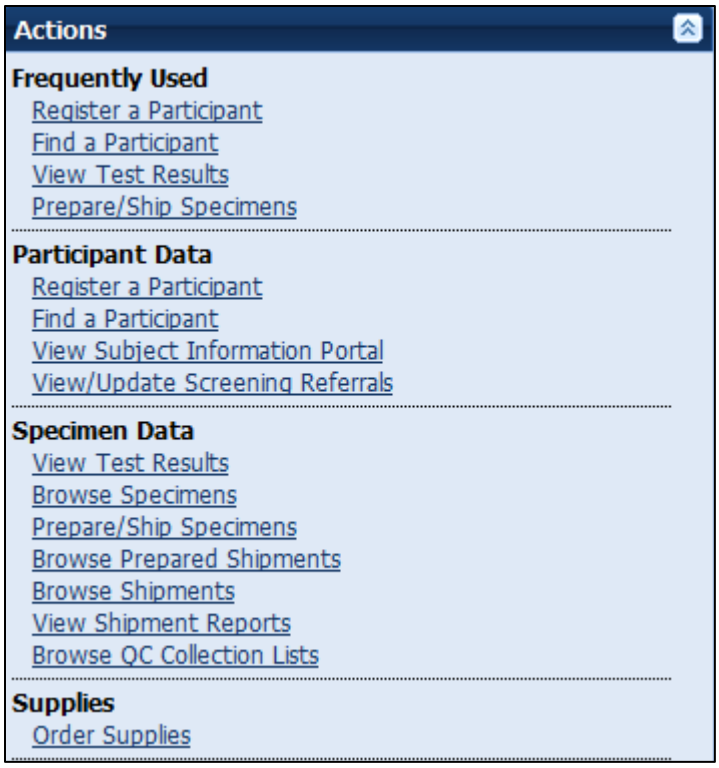


11.1.4 Archive

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

11.2 TN10 – Actions Portlet

From the TN10 – Anti-CD3 Prevention homepage, all study-related actions are available in the "Actions" portlet.



11.2.1 TN10- Frequently Used

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

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

11.2.2 Participant Data

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

1. Register a Participant
    a. This link takes the user to register a new participant for the study.
2. Find a Participant
    a. This link takes the user to locate a participant's record.
3. Assign Treatment
    a. This link takes a user to the "Assign Treatment" page where the user may randomize the participant in the system. Please note: a site should only randomize a participant in the system after the TNCC protocol CRA has confirmed the participant's eligibility for the study and has directed the site to randomize the participant in the system.
4. View Assigned Treatment Report

a. This link takes the user to view all of the assigned treatments for participants at their site.

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

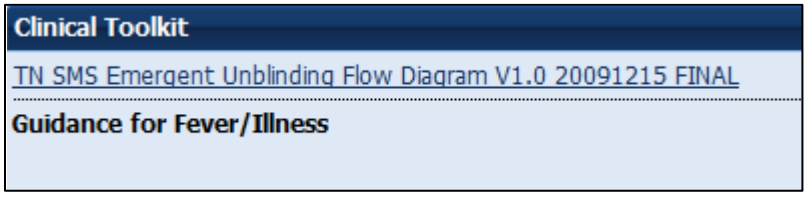
Under the "Supplies" actions header is a link to the Supply Ordering System (SOS).

11.3 TN10 – Contacts

From the TN10 – Anti-CD3 Prevention homepage, all study-related contacts are available in the "Contacts" portlet.

11.4 TN10 – Clinical Toolkit

From the TN10 – Anti-CD3 Prevention homepage, all study-related clinical tools are available in the "Clinical Toolkit" portlet.



11.5 TN10 – Calendar

From the TN10 – Anti-CD3 Prevention homepage, all study-related calls, trainings and event are noted in the "Calendar" portlet.

11.6 TN10 – Protocol Development Committees

From the TN10 – Anti-CD3 Prevention homepage, links to the Protocol Chair Committee and Study Group Committee pages are located under the "Protocol Development Committee" portlet.

11.7 TN10 – Publications

From the TN10 – Anti-CD3 Prevention homepage, all protocol specific publications, ancillary publications and data sharing policies are located under the “Publications” portlet.

11.8 TN10 – Frequently Asked Questions

From the TN10 – Anti-CD3 Prevention homepage, all protocol specific frequently asked questions (FAQs) are located under the “Frequently Asked Questions” portlet.

12. Member's Website Reports

12.1 Network Wide Reports

Step 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.

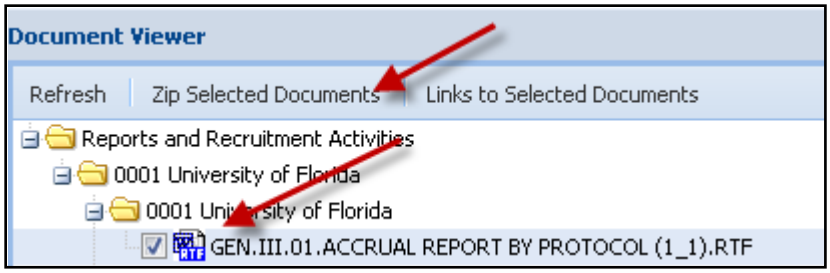
Step 3. Next, select the "General Reports" folder.

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 TN10 – Anti-CD3 Prevention homepage, all general and site specific reports are located under the "Reports and Recruitment" portlet.

12.2.1 Accessing Protocol Specific Reports

Step 1. To access reports with specific data for your individual site, from the TN10 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	TN10.I.01.Accrual Report By Clinical Center .rtf	Accrual totals, by clinical center	Monthly
	TN10.I.02.Actual.v.Expected Accrual - Graph.rtf	Graph of actual verses expected accrual.	Monthly
	TN10.I.03.IRB Summary - Ethnicity, Race and Gender Report.rtf	IRB summary of ethnicity, race and gender for all subjects	Monthly
	TN10.I.04.Adverse Event Summary Report.rtf	Summary of all reported AEs and SAEs	Weekly
	TN10.II.11. TN10-Anti-CD3 Eligibility Summary.rtf	Screening and Enrollment report by year	Weekly
Site Reports	TN10.III.01.Accrual Report By Institution (CC#).rtf	Accrual summary for clinical center and all affiliates	Monthly
	TN10.III.02.IRB Summary - Ethnicity, Race and Gender Report (CC#_Site#).rtf	Displays IRB summary of ethnicity, race and gender	Monthly
	TN10.III.03.Adverse Event Summary Report (CC#_Site#).rtf	Displays summary of all AEs and SAEs	Monthly
	TN10.III.09.Particpant Schedule of Visits Report (CC#_Site #).rtf	Displays a calendar of target dates for subjects' visits	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** – lifestyle questionnaires, scheduling wheels, TN01 teleforms, recruitment and retention materials, diabetes management supplies (if applicable).

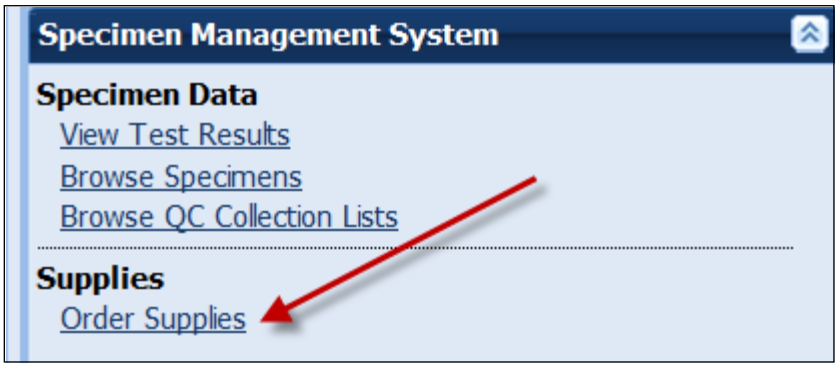
The TNCC reviews and approves all orders placed in the Fisher online system within 48 hours and, if applicable, contacts TradeWinds to fulfill etched vial orders. Some supplies are directly supplied by the USF TNCC, including lifestyle questionnaires, scheduling wheels, teleforms, and recruitment materials.

13.2 Ordering Supplies

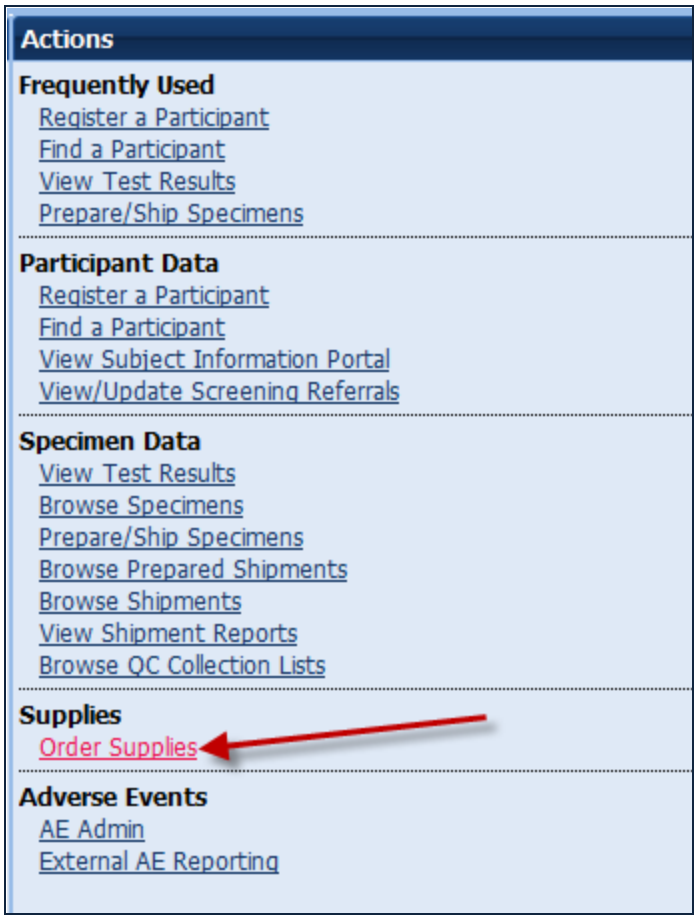
13.2.1 Navigating the Fisher BioServices Supply Ordering System (SOS)

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

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



From the TN10 – Anti-CD3 Prevention Study homepage, navigate to the central “Actions” portlet and select “Order Supplies.”

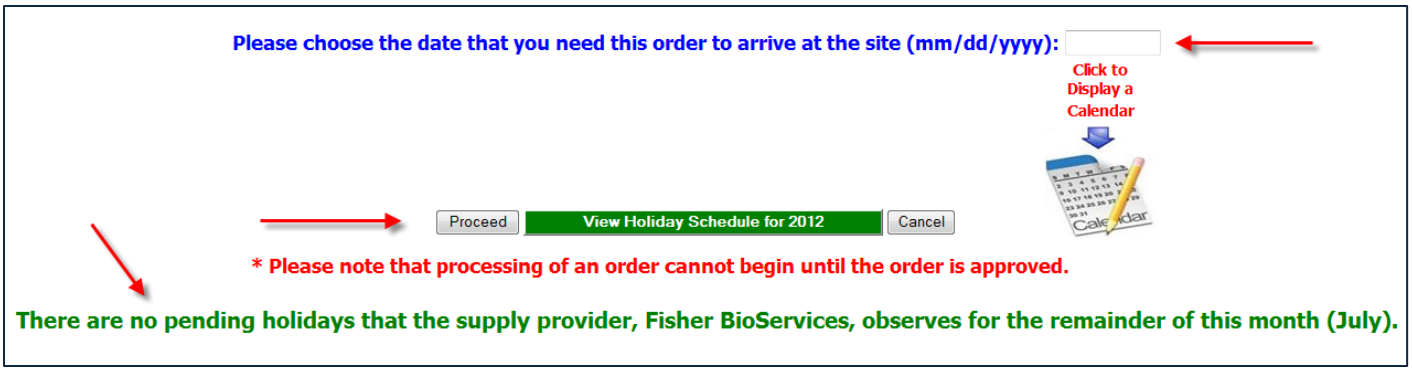


Step 2. The Supply Ordering System (SOS) web page will appear in a new window. You will be prompted to enter your TrialNet Supply Order System Login information.

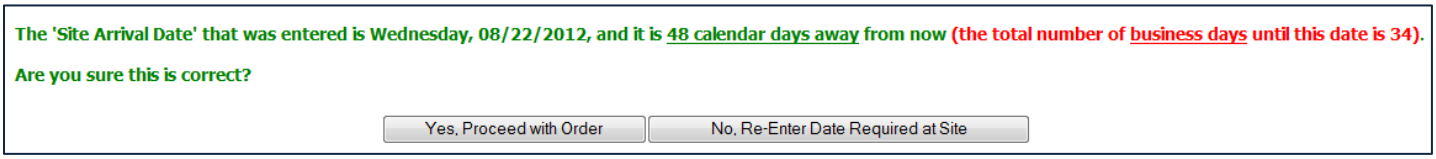
Note: If you do not have a login, please contact the TNCC to obtain a user account.

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.**

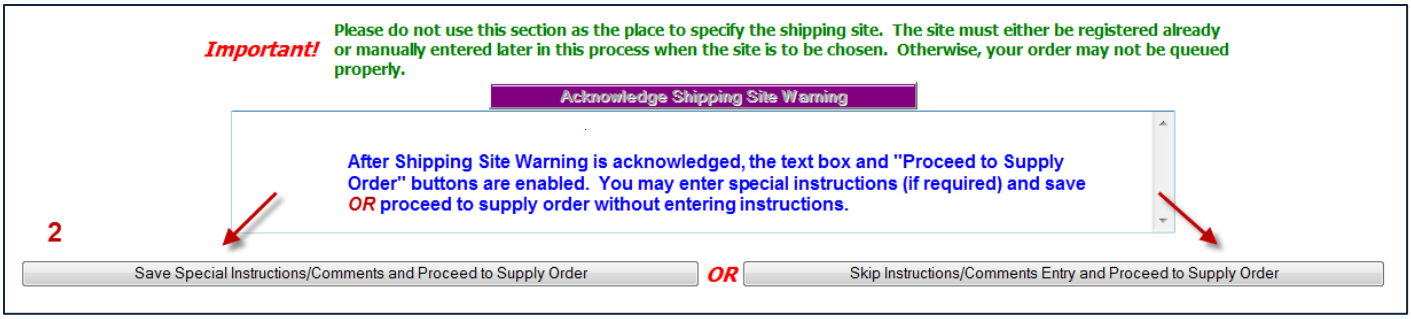


Step 5. After entering the date and selecting "Proceed" you will be prompted to confirm the date and either select proceed or opt to re-enter the date. If the date you have selected is OK, please select "Yes, Proceed with Order." If not then select "No, Re-Enter Date Required at Site."

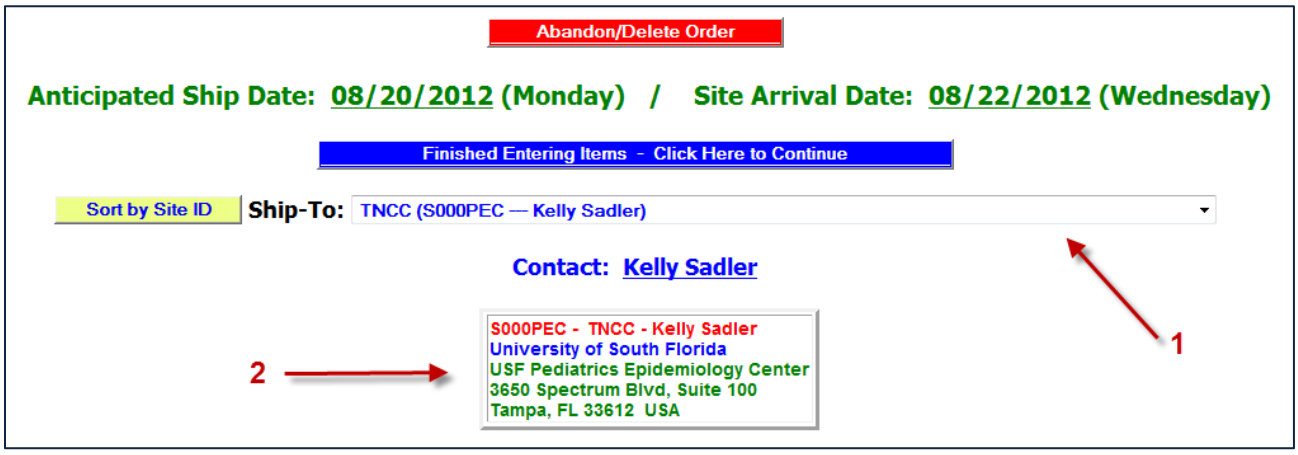


Step 6. Once you have confirmed the date is correct and selected "Yes, Proceed with Order" you will be prompted to enter order instructions or comments OR proceed to the order without special instructions:

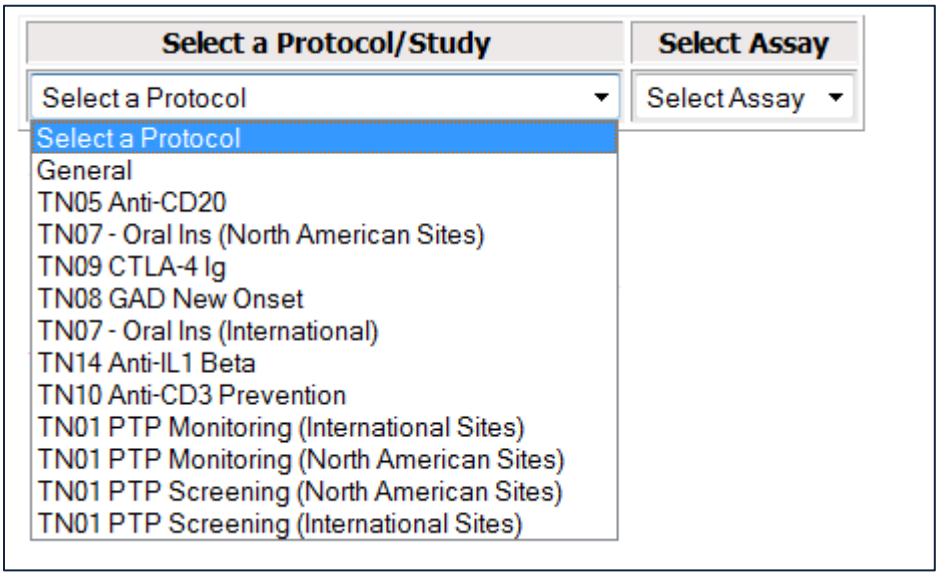
a. If you would like to enter special instructions, please enter them into the box provided and select "Save Special Instructions/Comments and Proceed to Supply Order."
b. If you do not have any special instructions or comments regarding the order, please select "Skip instructions/Comments Entry and Proceed to Supply Order."



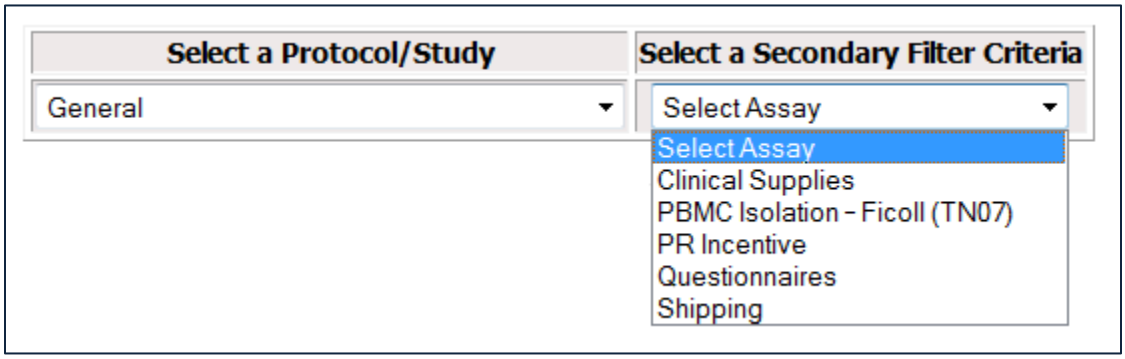
Step 7. Enter the “Ship to Site” by selecting a site from the “Ship-To” dropdown menu.



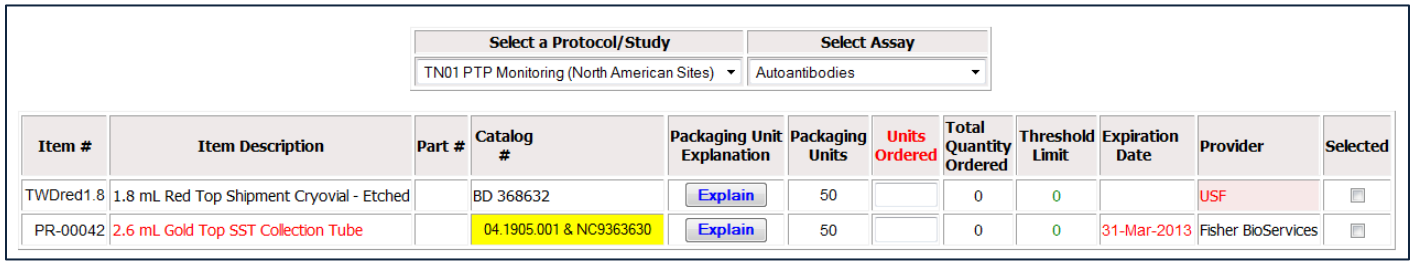
Step 8. Select the Protocol/Study and Assay for which you want to order supplies.



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
TWDred1.8	1.8 mL Red Top Shipment Cryovial - Etched		BD 368632	Explain	50		0	0		USF	
PR-00042	2.6 mL Gold Top SST Collection Tube		04.1905.001 & NC9363630	Explain	50		0	0	31-Mar-2013	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

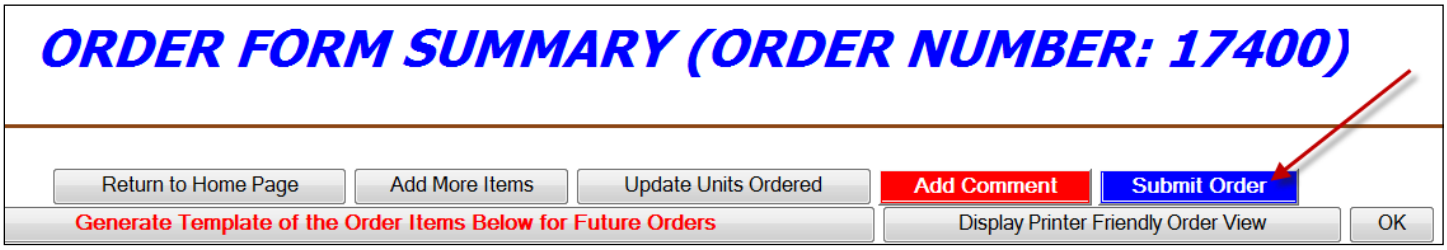
quantities. The "Total Quantity Ordered" field will update to reflect the total number of items that will be shipped.

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

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

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.

The table below lists all filter criteria applicable to the TN10 – Anti-CD3 Prevention Study.

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

TN10 – Anti-CD3 Prevention Supply Organization	
"Protocol" Filter Criteria	**"Test/Assay" Secondary Filter Criteria**
TN10 Anti-CD3 Prevention	CBC Chemistries EBV/CMV PCR EBV/CMV Viral Serology Glucose- Fasting or Random Handbooks HbA1c HIV/Hep B/Hep C INR Mechanistic Serum OGTT Questionnaires Remote Collection- Random Glucose Serum-Anti-Teplizumab Response Serum- PK Whole blood- PBMC/Plasma Whole Blood- RNA
General Supplies	Clinical Supplies Shipping PR Incentive Questionnaires

14. TNCC Audit Program

14.1 Components of an Audit Site Visit

1. Subject case records
2. Pharmacy operations and IND accountability
3. Regulatory compliance – IRB documentation and informed consent content
4. Laboratory operations.

14.2 Selection of Institutions/Investigators

14.2.1 Observational Studies

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

14.2.2 Prevention and Intervention Studies

All TrialNet interventional studies will be audited.

1. For domestic sites, studies will be eligible for an audit site visit within 6 months of the fifth subject accrual and annually thereafter.
2. For international sites, studies will be eligible for an audit site visit within 6 months of the first subject accrual and annually thereafter.
3. If an institution is withdrawn or terminated from TrialNet and the continued long-term follow-up of enrolled subjects is required per protocol(s), the investigator is expected to collect good quality data according to the study(ies) schedule. These studies remain eligible for audit site visits.
4. If audit findings require follow-up to assess resolution of problems identified at a previous audit, a re-audit may be conducted (usually at 3-6 months after a routine audit or sufficient subject accrual). If the re-audit findings are acceptable, the next full audit will be scheduled within 6-12 months of the successful audit date.

14.3 Audit Teams

1. The auditor(s) will be selected by the TNCC and will be suitably qualified for the types of studies being audited. They will be knowledgeable about clinical trials methodology, NIH policies, and Federal regulations.
2. Local IRB representatives may observe the audit.
3. An NIH representative or other members appointed by the TN Executive Committee may elect to be present at an audit to monitor the audit process and to ensure that TN and the NIH's monitoring guidelines are being met.

14.4 Arranging the Audit

1. An audit date mutually convenient to the audit team and the site will be selected.
2. A confirmation email, including the TNCC audit confirmation letter, audit agenda, audit information sheet and TNCC audit guidelines will be sent to the site no less than 30 days in advance of the audit site visit.
3. A list of announced cases will be sent to the site no more than 14 days in advance of the audit site visit
4. The Principal Investigator and a CRA at the institution being audited, who is familiar with the selected cases, must be available on the date(s) selected.
5. The length of an audit depends on the number of cases being reviewed and which areas will be audited (i.e. pharmacy, regulatory compliance, IRB). Audits will usually last between a minimum of 4 hours and a maximum of 2 days.
6. The site is responsible for ensuring that all relevant materials are available for review at the time of the audit.

14.5 Selection of Cases

The TNCC will select all cases for all audits.

1. Approximately 10% of the total cases accrued at the site on TrialNet studies – with a minimum of 5 and a maximum at auditor discretion - will be audited. If 5 or fewer subjects have been accrued at the site, then all cases will be audited.
    a. All annual audits will include one unannounced case
    b. If an audit of unannounced cases is warranted during an initial site visit, at least one or more additional cases will be selected at the time of the audit visit.
    c. Unannounced cases may have a limited audit consisting at a minimum of informed consent and eligibility. If the unannounced cases only receive a limited review, then these cases do not count towards the minimum of 10%.

14.6 Preparation by the Institution being Audited

1. The site is required to provide source documents, research charts, IRB documents (and, if applicable, x-rays or scans) in a work area for the audit staff. The source documents should be labeled to correspond with the subject research documents. A member of the site staff should be available to answer questions from the audit team for the duration of the audit site visit.
2. An exit interview will be conducted by the audit team leader with the TrialNet site Principal Investigator and TrialNet site staff at the conclusion of the audit.
3. Final audit results will be forwarded to the TrialNet site Principal Investigator, the Clinical Monitoring Group and the NIH within 12 weeks of the audit.

Items that should be provided at the audit include:

1. Orientation by the site staff to the organization of the source documents and case report forms (research study charts)
2. Suitable location for auditors to conduct their review. This location should allow the auditors privacy to conduct their review. It should be secure so that auditors' laptops and belongings are safe. It should have access to the internet (wired or wireless) or allow the auditors to utilize their wireless internet cards. Please note that some physical locations at your site may interfere with wireless card transmission. Please notify the TNCC if a location that provides internet access is not available.
3. Original source documents for each subject being audited
4. All subject consent forms
5. Documentation of IRB approval for all protocols being audited, including: original protocol approval, all amendment approvals, and annual re-approval
6. Most current copy of each protocol with all addenda
7. A visit to the pharmacy should be scheduled by the site staff for audits of studies utilizing drug(s) dispensed by a pharmacy at the site. Drug logs should be available for review. The institution should be using the NCI Drug Accountability Record Form or the institution approved equivalent.
8. If the drug(s) is not dispensed by a pharmacy at the site but by the study team, the drug ordering, handling and storage procedures must be shown to the audit team.
9. Source documentation should be organized so that auditors can easily identify them.

14.7 Required Documents

14.7.1 Regulatory Documents

Essential documents including:	• Principal Investigator and sub-investigators' Curriculum vitae • Principal Investigator 1572 • Proof of Human Subject Protection education training for PI and all research staff handling subject data • Site Delegation Log • Letters of initial and continuing IRB approval • IRB committee composition (roster) • Required regulatory authority's(ies') authorization/approval • Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) that are locally obtained • Certification/accreditation for medical/laboratory/technical procedures/tests at start of the study and updates during the conduct of the study for local labs. • Important sponsor and/or TNCC correspondence including: letters, meeting notes, notes of telephone calls • Subject identification list – list of all subjects entered on the study with their sequence number • Subject screening / identification logs, as applicable
Original IRB submission including:	• Advertisement(s) to recruit subjects • Informed consent • Any other written information provided to subjects • Study agent Investigator's Brochure or package insert (if request by IRB for submission) • Case report forms (if request by IRB for submission)
Protocol amendment submission:	• Amended protocol • Amended informed consent • Any other amended written information provided to subjects • Amended advertisement(s) • Amended case report forms (if request by IRB for submission)
All IRB correspondence including:	• Annual renewal/continuing reviews • Updates to Investigator's Brochure • Adverse event reporting • Acknowledgement of DSMB reports
Study agent documentation including:	• Receipts sent with shipment of study agent • Study agent accountability logs that reflect log in of study agent shipments • Study agent accountability logs that reflect each time study agent is dispensed • Study agent accountability logs that reflect return or destruction of unused study agent • Sample of label(s) attached to investigational product container(s) (what the subject sees) • * Procedures for unblinding trial, if applicable • * Master randomization list, if applicable

14.7.2 Source Documents

Acceptable source documentation includes, but is not limited to:	• Laboratory results • Quality of Life forms • Physician or staff dictation • Nursing notes • Medication records • Consults • Hospital, clinic, or office medical records • Notes to file • TrialNet site research charts • Signed specimen shipment logs • Subject diaries and/or calendars • Food diaries • Progress notes • Demographic forms • Pathology reports • Radiology reports • Operative reports • Worksheets within the medical record charts

1. Good standard of practice for source documentation includes:
    a. Subject PID legible on all documents
    b. All entries are legible and signed by staff
    c. All entries are made in ink or are typewritten
    d. Data corrections as follows:
        i. Do not ablate incorrect information. Use a strike through so that original information is still legible.
        ii. Write the date that the document is changed.
        iii. Include initials of the person making the change.
        iv. If corrected information cannot be inserted so it is legible, insert an addendum page with the correction.
        v. Reports officially issued by a department such as radiology or pathology may only be changed by that department. Changes must be reflected in an officially issued amended report.
        vi. Documentation with erasures or use of correction tape/fluid is not acceptable.

14.8 Record Retention

14.8.1 IRB records [45 CFR 46.115(b) and 21 CFR 56.115]

The records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the department or agency at reasonable times and in a reasonable manner.

14.8.2 Study agent records [21 CFR 312.57©] [21 CFR 312.62©]

A sponsor shall retain the records and reports required by this part for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigation use is discontinued and FDA has been so notified.

14.9 Data Reconciliation

Auditors will review source documentation and compare it to data submitted on case report forms. Auditors will identify any discrepancies found between source documentation and case report forms to the TrialNet study site.

14.10 Data Delinquency

The TNCC will monitor data delinquency on an ongoing basis. Investigators will be queried for missing data forms that are not received within 30 days of the due date. The rate of data delinquency will be reviewed at the time of audit. Persistent data delinquency may be considered a violation.

14.11 Audit Results

1. A Major violation is a protocol variance that makes the resulting data questionable.

2. A Minor violation is deviation that does not affect the outcome or interpretation of the study, and is not described as a major violation. An unacceptable frequency of lesser deficiencies will be treated as a major deficiency in determining the final assessment of a component.

14.11.1 IRB Documentation / Study Conduct

Major violations include but are not limited to:	1. Protocol never approved by IRB 2. Initial IRB approval documentation missing 3. Inappropriate initial approval by expedited review [45 CFR 46.110 non-compliance] 4. Registration and/or treatment of subject prior to full IRB approval (initiation of study related procedures prior to IRB approval) 5. Registration of subject on protocol during a period of delayed re-approval 6. Reportable adverse events not reported to IRB 7. Lack of IRB approval of a protocol amendment.

14.11.2 Informed Consent

Omissions of one or more of the elements required by federal regulations 21 CFR 50.25 / 45 CFR 46.116:	1. Statement that the study involves research 2. Explanation of the purposes of the research 3. Expected duration of the subject's participation 4. Description of the procedures to be followed 5. Identification of any procedures which are experimental 6. Description of any reasonably foreseeable risks or discomforts to the subject 7. Description of any benefits to the subject or to others which may reasonably be expected from the research 8. Disclosure of appropriate alternative procedures or courses of treatment (if any) that may be advantageous to the subject 9. 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 10. For research involving more than minimal risk, an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained 11. 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 12. 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 major violations:	1. Omissions of multiple risks / side effects as listed in the model informed consent document and/or in subsequent serious adverse event reports 2. Multiple/cumulative effect of minor problems for a given informed consent
Additional consent form issues:	1. Consent form missing 2. Consent form not signed & dated by subject 3. No documentation that consent was given and the form was signed by the subject prior to protocol-related studies or procedures 4. Consent form is missing signatures 5. Consent form not current IRB-approved version at time of subject enrollment 6. Consent form not protocol-specific 7. Consent form doesn't include updates or information as required by IRB 8. Consent obtained in wrong language

14.11.3 Subject Case Records:

Eligibility:	1. Protocol specific eligibility requirements not met 2. Missing source documentation of eligibility requirements
Treatment administration:	1. Incorrect study agent/treatment used 2. Additional agent used which is not permitted by that protocol 3. Dose calculated incorrectly 4. Dose modifications not justified 5. Treatment doses incorrectly administered, calculated or documented

Toxicity:	1. Failure to assess toxicities and adverse events according to protocol 2. Grades, types or dates/duration of serious toxicities inaccurately recorded 3. Toxicities cannot be substantiated 4. Follow up procedures necessary to assess toxicities not performed 5. Failure to report toxicity and adverse events
Data quality:	1. Recurrent missing source documentation to support data points on CRFs 2. Protocol specific laboratory or radiology tests not documented 3. Frequent and recurrent data inaccuracies 4. Frequent and recurrent errors in submitted data

14.11.4 Pharmacy Operations:

Accountability and storage of Study Agent:	1. Study agent not stored separately by protocol 2. Study agents not stored under proper conditions 3. Study agent stored in insecure dispensing area 4. Inability to track receipt, use and disposition of study agent per protocol 5. Study agent transferred between sites with adherence to TN transfer policies 6. Study agent used for non-registered subjects 7. Multiple drug accountability records incomplete and/or not kept up on timely basis 8. Drug accountability records routinely filled out incorrectly (e.g. Incorrect agent, dose, route of administration, or dates documented)

14.12 Final Audit Categories

Acceptable	1. No deficiencies identified 2. Few lesser deficiencies identified 3. Major deficiencies identified that were addressed and/or corrected PRIOR to the audit completion
Acceptable, Needs Follow-Up	1. Multiple lesser deficiencies identified 2. Major deficiencies identified during the audit not corrected and/or addressed prior to audit completion
Unacceptable	1. Multiple major deficiencies identified 2. Single flagrant major deficiency identified 3. Multiple lesser deficiencies of a recurring nature found in a majority of the subject cases reviewed

1. **Acceptable** assessments do not need a response from the investigator.

2. **Acceptable, Needs Follow-Up** assessments require a written response from the TrialNet site Principal Investigator within 2 weeks of the receipt of the audit assessment letter. The reply must address each specific problem found during the audit and any general problems that were noted. The reply must include a corrective plan that details communication, education, staffing changes or other internal measures taken to ensure that deficiencies do not occur. A copy of the written response and corrective action plan will be forwarded to the Study Chair, the TNCC Principal Investigator, Clinical Monitoring Group and the NIH in the Final Report. A follow-up re-audit may be required.

3. **Unacceptable** assessments require a written response from the TrialNet site Principal Investigator within 2 weeks of the receipt of the audit assessment letter. The reply must address each specific problem found during the audit and any general problems that were noted. The reply must include a corrective plan that details the communication, education, staffing changes or other internal measures taken to ensure that deficiencies do not occur. A copy of the written response and corrective action plan will be forwarded to the Study Chair, the TNCC Principal Investigator, Clinical Monitoring Group and the NIH in the Final Report. Re-audit is mandatory for all unacceptable assessments.

14.13 Special Audits

Special audits may be warranted when there are significant irregularities found through quality control procedures or when allegations of scientific misconduct are made. It is the responsibility of the TNCC to immediately notify the NIH if they learn of any significant irregularities or allegations related to scientific misconduct by a staff member or institution participating in their research program. Selection of auditors to conduct special on-site audits will be made jointly by the NIH, and the TNCC, and a joint course of action will be planned. Other Federal agencies or offices may be invited to participate in a special audit at the discretion of the NIH.

14.14 Audit Reports

1. During the audit, forms to document those present at the audit and details of the studies and cases reviewed will be completed and retained in the TrialNet site's file. Any problems or concerns regarding compliance or data validity, accuracy or completeness will be noted. Any suspicion of scientific misconduct will be reported immediately to the NIH.
    a. <u>Preliminary Report of Audit Findings:</u>
    This form documents major deficiencies in regulatory, pharmacy or subject cases. It will be e-mailed to the NIH and the Clinical Monitoring Group within 24 hours of leaving the audit site if major deficiencies are found at the site. This report will be copied to the Site Principal Investigator, the Site Study Coordinator and the TNCC Principal Investigator.

    b. <u>Report of Audit Findings:</u>
    A narrative summary letter outlining the findings of the audit will briefly summarize overall findings of IRB approval, informed consent content, study agent handling and accountability and contents and accuracy of subject records. Deficiencies found during the audit will be discussed and a description of any corrective plans will be noted. The exit interview will be summarized. The audit team's overall assessment of the audit and recommendations for the next audit will be included with the notation that it is pending NIH and Clinical Monitoring Group review. This report is due within 10 working days of the audit to the TrialNet site Principal Investigator. This report will also be sent to the NIH, the Clinical Monitoring Group, the Study Chair, the TNCC Principal Investigator and the Site Study Coordinator.

    c. <u>Final Report of Audit Findings:</u>
    A narrative summary letter outlining the findings of the audit will briefly summarize overall findings of IRB approval, informed consent content, study agent handling and accountability and contents and accuracy of subject records. Deficiencies found during the audit and any corrective action will be discussed and a description of any further corrective plans will be noted. The exit interview will be summarized. Audit team assessment and recommendations for the next

audit interval will be reported. A copy of any responses by the TrialNet site Principal Investigator will be included in the Final Report. This will be completed and sent to the TrialNet site Principal Investigator within 12 weeks of the audit. A copy of the final report will also be sent to the NIH, the Clinical Monitoring Group, the Study Chair, the TNCC Principal Investigator and the Site Study Coordinator.

References:

NIH NCI-CTMB Guidelines for monitoring of clinical trials for cooperative groups: http://ctep.info.nih.gov/monitoring/2006_ctmb_guidelines.pdf
Required Study Documentation: E6 GCP ICH 8.2
IRB records [45 CFR 46.115(b) and 21 CFR 56.115]
Study agent records [21 CFR 312.57(c)] [21 CFR 312.62(c)]
Requirements for Expedited IRB approval (45 CFR 46.110)
Subject recruitment and advertising documentation (21 CFR 50.20, 50.25, 56.111(a)(3) and 812.20(b)(11)
Informed Consent Requirements: 21 CFR 50.25 and 45 CFR 46.116

14.15 Monitoring Visits

In addition to the audit visits this study will have an additional monitoring component that is separate from the auditing visits. The documents listed in section 13.7 will also be required for all monitoring visits.

14.15.1 Case Selection

All enrolled participants, and data verification for 100% of the data points collected on this protocol will be monitored at each site. At all visits after the initial visit, follow-up action items noted on the previous site visit will be checked, in addition to any new data entered since the previous visit.

14.15.2 Visit Timeline

The initial visit will be triggered after the site enrolls the first participant. The TNCC monitor will contact the site to setup the initial site visit on a mutually convenient date post infusion of the participant.

After the initial visit, all subsequent visits will occur after another participant is enrolled and has completed their infusion. Sites will have a maximum of 1 monitoring site visit every quarter. If possible, every effort will be made to combine the monitoring visit with the audit site visit.

14.15.3 Visit Reports

Two reports will be used to communicate the results of the monitoring visit. The summary report will list general site study updates and any major concerns found by the monitor. The detailed report will list any requested action items to be performed by the site. This will include any data queries, IRB submission follow-up, and pharmacy errors. All action items should be completed prior to the next monitoring visit. Both monitoring visit reports will only be sent to the site PI, site coordinator, and members of the TNCC.