Protocol TN07

Oral Insulin for Prevention of Diabetes in Relatives at Risk for Type 1 Diabetes Mellitus

Desmond Schatz, MD

Manual of Operations
Version 6.0 20Feb15

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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 (01Nov12)

Title	*Oral Insulin For Prevention Of Diabetes In Relatives At Risk For*
IND Sponsor	*Type 1 Diabetes Mellitus*
Conducted By	Type 1 Diabetes Trial Network (TrialNet)
Protocol Chair	Desmond Schatz, M.D.; University of Florida, Gainesville, FL.
Accrual Objective	A fixed target sample size has not been specified. Rather, the study is designed as a maximum information trial in which subjects are recruited and followed until the required amount of statistical information is achieved that provides 85% power to detect a 40% risk reduction using a one-sided logrank test at the 0.05 level.
Study Design	The study is a 2-arm, multicenter, randomized, double-masked, placebo-controlled clinical trial.
Treatment Description	Subjects will receive oral insulin 7.5 mg of recombinant human insulin crystals or placebo in capsules.
Objective	The primary objective is to determine whether intervention with oral administration of recombinant human insulin given on a daily basis will prevent or delay the development of clinical Type 1 Diabetes Mellitus (T1DM) in subjects at risk for T1DM.
Primary Outcome	The primary outcome is the elapsed time from random

	treatment assignment to the development of diabetes among those enrolled in the primary analysis cohort consisting of subjects with insulin autoimmunity and absence of metabolic abnormalities. Criteria for diabetes onset are as defined by the American Diabetes Association (ADA) based on glucose testing, or the presence of symptoms and unequivocal hyperglycemia.
Major Inclusion Criteria	(1) Relatives of T1DM proband with mIAA and at least one other islet autoantibody present (2) Normal OGTT performed within 7 weeks prior to randomization. The primary analysis stratum and secondary analysis strata are defined based on combinations of other autoantibodies present, and presence or absence of first phase insulin response on IVGTT.

1.3 Study Contacts

TN07 Oral Insulin Study TrialNet Coordinating Center (TNCC)		
USF TrialNet Coordinating Center (TNCC) University of South Florida Health Informatics InstituteTampa, FL 33615	Primary Contact: Nichole Reed	Ph.: (813) 396-9461 Fax: 813-910-1245 Email: Nichole.Reed@epi.usf.edu
	Secondary Contact: Courtney Henderson	Ph.: (813) 396-9541 Fax: 813-910-1246 Email: Courntey.Henderson@epi.usf.edu

TN07 Oral Insulin 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

TN07 Oral Insulin Study Core Laboratories
Please refer to the TN07 Oral Insulin Study Laboratory Manual for a complete list of TrialNet Core laboratories applicable to the TN07 protocol.

For participating site contact information please refer to TN07 Contact Portlet located on the bottom of the protocol homepage of the member's 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.

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. 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

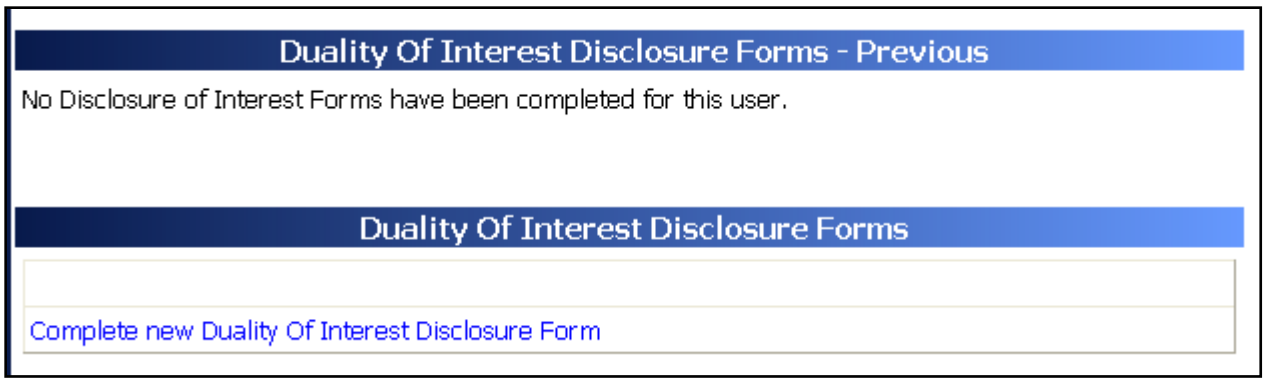
Site activation will require a completed duality of interest form from a minimum of both the PI and main site coordinator.

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:

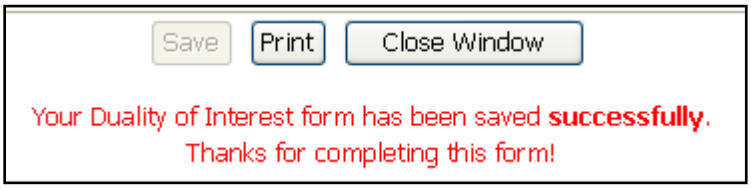
Step 1. From the main TrialNet members' web site, under the Calendar in the "Administration" portlet, click on the link "Complete/Update Duality Form."

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.

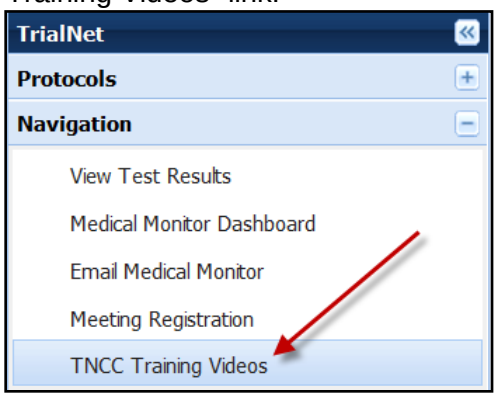
3.5 Study/System Training

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

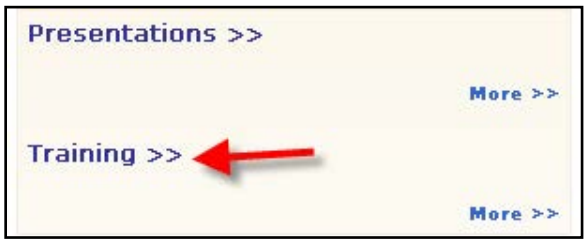
3.5.1 Online Training

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:

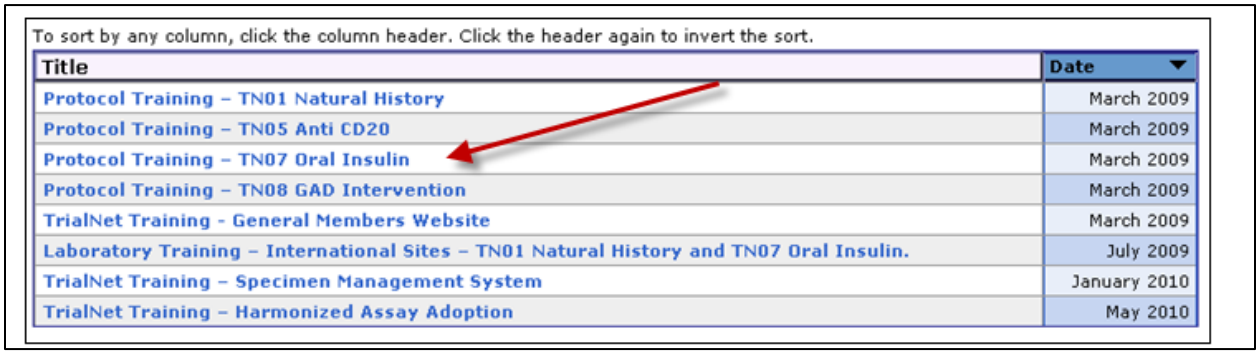
Step 1. From the main TrialNet members' website, on the left side navigation bar, click on the "TNCC Training Videos" link.



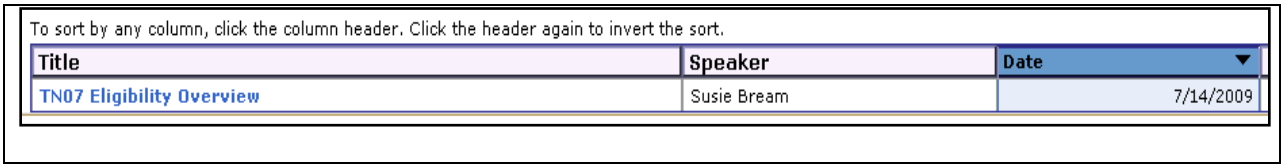
Step 2. A new window will open to the media center. Click on the "Training" link.



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) TN07 Eligibility Overview: Reviews inclusion and exclusion criteria for the Oral Insulin Study as well as frequently asked questions for each. Also reviews study endpoint and definition of Diabetes.

2) TN07 IVGTT Training: Explains the proper procedures for performing the IVGTT. It also includes a brief review of OGTT and MMTT testing procedures.

3) TN07 TrialNet Abdominal Circumference Training: Provides the proper procedures for measuring abdominal circumference at study visits.
4) TN07 Follow-Up Visit Pharmacy Procedures: Reviews the procedures for study drug return and dispensation at follow-up visits.

3.5.2 TN07 Study Protocol Certification Quiz

The TN07 Oral Insulin Study 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. The quiz is posted online on the TN07 Oral Insulin protocol page under “Working Documents” under the “Training Documents” link in the “Certification Quizzes” folder. Once the certification quiz has been completed the site can request the answers from their clinical center to review.

3.5.3 TN07 IVGTT Test Quiz (General Tolerance Test Quiz and Specific Quiz)

The IVGTT Certification Quiz and the General Tolerance Test Quiz is a training resource available for all site members that will be administering tolerance tests to subjects. These quizzes are posted online on the TN07 Oral Insulin protocol page under “Working Documents” under the “Training Documents” link in the “Certification Quizzes” folder. Once the certification quiz has been completed the site can request the answers from their clinical center to review.

3.5.4 TN07 Oral Insulin Pharmacy Certification Quiz

The Oral Insulin Pharmacy Certification Quiz is available online and is specific to the Oral Insulin Study pharmacy procedures. The quiz is a training resource available for sites to become more familiar with the Oral Insulin pharmacy procedures. The quiz is posted online on the TN07 Oral Insulin protocol page under “Working Documents” under the “Training Documents” link in the “Certification Quizzes” folder. 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

A fixed target sample size has not been specified and the date on which the study will terminate has not been fixed in advance. Rather, the study is designed as a maximum information trial in which subjects are recruited and followed until the required amount of statistical information is achieved that provides 85% power to detect a 40% risk reduction using a one-sided logrank test at the 0.05 level. The required information number is I = DO*DC/(DO + DC) = 27.6; where DO, DC are the observed numbers developing diabetes in the oral insulin and control groups, respectively. Thus, the exact total sample size and study duration are unknown.

Projected recruitment goal: 50 to 60 subjects annually for 10 years.
Activation date: February 7, 2007

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:

The participant MUST:

1. Have a proband with T1DM. A proband is an individual diagnosed with diabetes before age 40 and started on insulin therapy within 1-year of diagnosis. Probands considered to have type 1 diabetes by their physician who do not meet this definition will be referred to the TrialNet Eligibility Committee
2. If the proband is a first degree relative (i.e. sibling, parent or a child), the study participant must be 3 - 45 years of age. If the proband is a second or third degree relative (i.e. niece, nephew, aunt, uncle, grandparent, cousin), the study participant must be 3-20 years of age. (Age criteria apply to the subject's age at the time of randomization). See Appendix B for further clarification regarding the definition of a proband).
3. Willing to give informed consent demonstrated by singing the Informed Consent Form.
4. Have normal glucose tolerance on an OGTT performed within 7 weeks (52 days) prior to randomization in which:
    a. Fasting plasma glucose < 110 mg/dL (6.1 mmol/L), AND

   b. 2-hour plasma glucose < 140 mg/dL (7.8 mmol/L), AND
   c. 30, 60, and 90 minute plasma glucose < 200mg/dL (11.1 mmol/L)
5. If previous abnormal glucose tolerance, has had two consecutive OGTT with normal glucose tolerance. One of which occurred within 7 weeks (52 days) prior to randomization.
6. mIAA confirmed positive within the previous six months (210 days). The initial presentation of a positive mIAA may occur at time in the Natural History/Pathway to Prevention Study. The confirmation of a positive mIAA must occur within 6 months (210 days from the date of the blood draw) of randomization in the Oral Insulin Trial
7. Two samples with at least one autoantibody *other than* mIAA positive within the previous six months. Additional autoantibodies are ICA, ICA512, or GAD65. Eligibility for the Oral Insulin Trial is based on testing positive for **any combination of two of these autoantibodies**. The initial positive sample of ICA, ICA512, or GAD65 may occur at any time in the Natural History/Pathway to Prevention Study. The second positive result may be of the same or a different autoantibody than the first positive result and must be within 6 months (210 days from the date of the blood draw) of randomization into the Oral Insulin Trial.

******Autoantibody eligibility for the Oral Insulin Study is based on the Standard Assay Only (Not the Harmonized Assay). Please review the "TrialNet Harmonized Assay Adoption and Oral Insulin BAA Eligibility" training located in the online Media Center and the Oral Insulin Training Materials folder.***

Exclusion Criteria:

The participant is not eligible if:

1. Does not satisfy the above inclusion criteria.
2. Has severe active disease, e.g. chronic active hepatitis, severe cardiac, pulmonary, renal, hepatic, immune deficiency and/or disease that is likely to limit life expectancy or lead to therapies such as immunosuppression during the time of the study.
3. Prior participation in a clinical trial for secondary prevention of T1DM (i.e. nicotinamide, insulin, immunosuppressive drugs).
4. Prior randomization to a prevention trial such as the Diabetes Prevention Trial (DPT). Note that exclusion only applies to a participant having been randomized. If a participant was screened only in DPT (i.e., not randomized), that participant is still eligible for the Oral Insulin Trial.
5. History of treatment with insulin or oral hypoglycemic agent. Any prior treatment with insulin, even if only one-time use, excludes an individual from participating in the Oral Insulin Trial.
6. History of therapy with immunosuppressive drugs or non-physiologic glucocorticoids within the past two years for a period of more than three months. If medications are begun AFTER being randomized into the Oral Insulin Trial they will be tracked on a regular basis using case report forms and source documents, but the participant will not be discounted from study participation.
7. Ongoing use of medications known to influence glucose tolerance, i.e. sulfonylureas, growth hormone, metformin, anticonvulsants, thiazide or potassium depleting diuretics, beta adrenergic blockers, niacin. Antipsychotics that have been reported to influence

glucose include apripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone. Other medications that significantly affect glucose are all oral hypoglycemic drugs, all forms of insulin, amylin (symlin), GLP mimetics [e.g. exenatide (Byetta), DPP-IV inhibitors], and steroids. These would all be excluded. Subjects on such medications should be changed to a suitable alternative, if available, and will become eligible one month (30 days) after medication is discontinued. If medications are begun after enrolling in the Oral Insulin Trial they will be tracked on a regular basis using case report forms and source documents, but the participant will not be discontinued from study participation.

8. Pregnant or intends to become pregnant while on study or lactating. A urine pregnancy test will be conducted on females of childbearing potential at the Initial Visit, 3-month Visit, 6-month Visit, and semi-annually until the completion of the study. If the participant has plans to become pregnant during the course of the study she should be excluded from participation. A urine pregnancy test will be conducted at each study visit to determine pregnancy.
9. Deemed unlikely or unable to comply with the protocol.
10. OGTT that reveals abnormal glucose tolerance unless two subsequent consecutive OGTT have normal glucose tolerance. Abnormal glucose tolerance is defined as:
    a. fasting plasma glucose ≥110 mg/dL (6.1 mmol/L), AND/OR
    b. 2 hour plasma glucose ≥ 140 mg/dL (7.8 mmol/L) AND/OR
    c. 30, 60, or 90 minute plasma glucose ≥ 200 mg/dL (11.1 mmol/L)
11. Subject has HLA DQA1*0102, DQB1*0602 haplotype.

Please review the following training documents available online regarding eligibility and identifying potentially eligible participants:

- Progression from TN01 to TN07 Training Slides 02 TN07 Progression From TN01 to TN07 Training Slides for Sites 01Nov12
- Eligibility Overview 03 TN07 Eligibility Overview 01Nov12
- Navigating to and interpreting the List of Potentially Eligible TN07 Participants 04 TN07 Interpreting the List of Eligible TN07 Participants Report 01Nov12
- TN07 Frequently Asked Participant Questions TN07 Oral Insulin Study Frequently Asked Questions

4.4 Rationale for Inclusion and Exclusion Criteria

These criteria have been selected to target a population at moderate risk for the development of type 1 diabetes.

4.5 Exceptions to Questions Regarding Eligibility Criteria

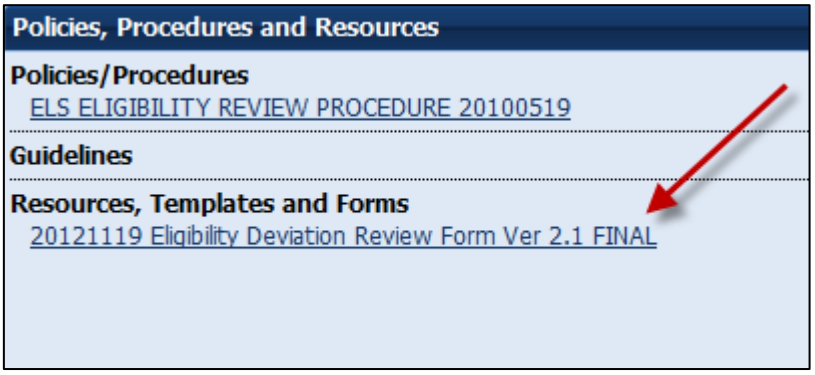
The TrialNet Coordinating Center will be responsible for initially reviewing and adjudicating any instances where eligibility is unclear. If following this initial review eligibility is still unclear, the TrialNet Eligibility Committee will review and adjudicate the situation.

4.5.1Procedures for submission to the TrialNet Eligibility Committee

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

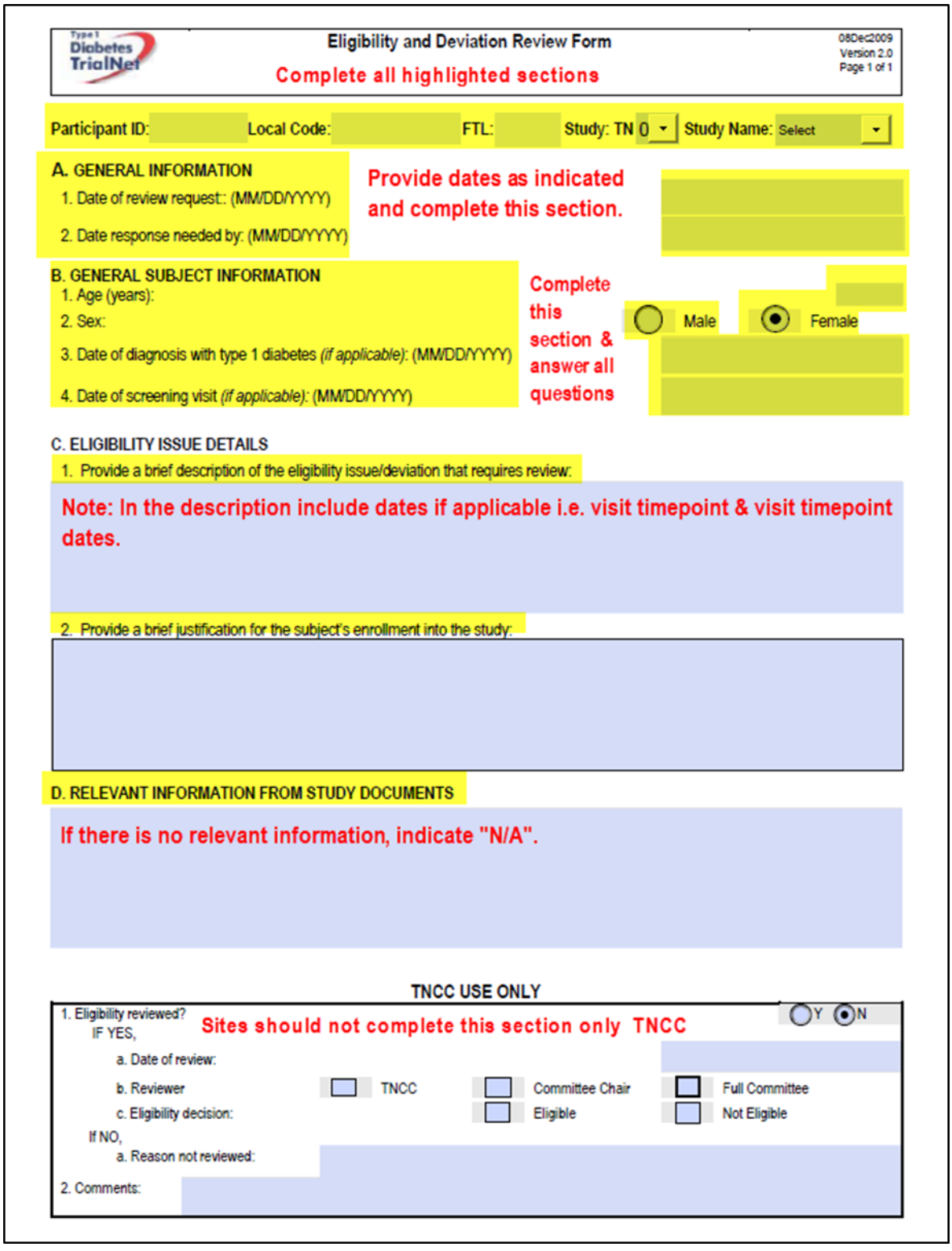
Step 1. Contact the TNCC CRA to review the question or matter regarding eligibility if unclear in the protocol

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

08Dec2009
Version 2.0
Page 1 of 1

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

Sites should not complete this section only TNCC

IF YES,
- a. Date of review:
- b. Reviewer TNCC Committee Chair Full Committee
- c. Eligibility decision: Eligible Not Eligible

If NO,
- a. Reason not reviewed:

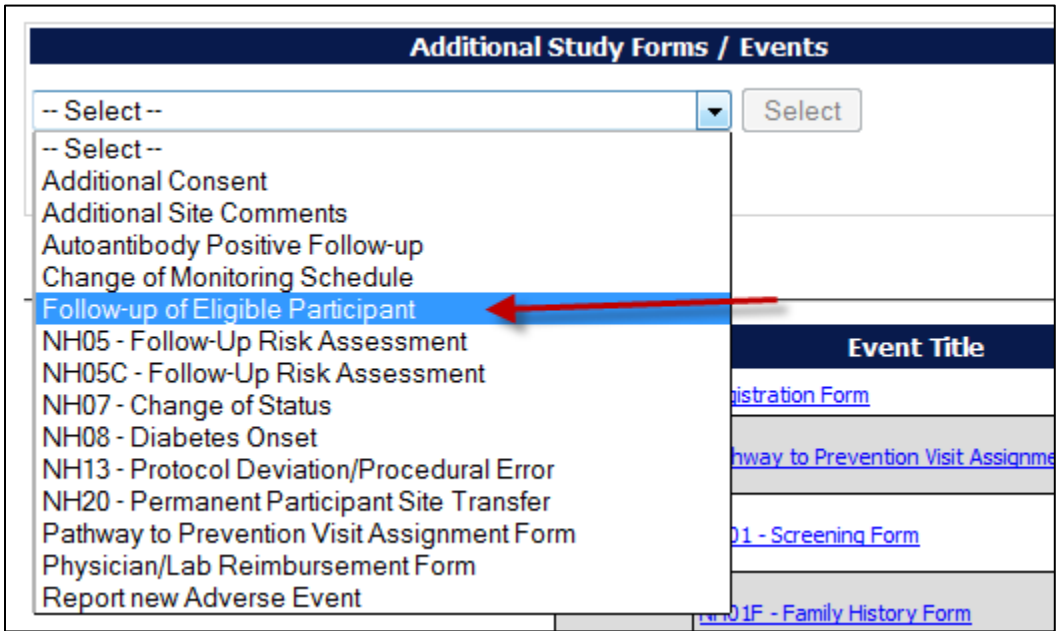
2. Comments:

4.6 Follow-up of Eligible Study Participant

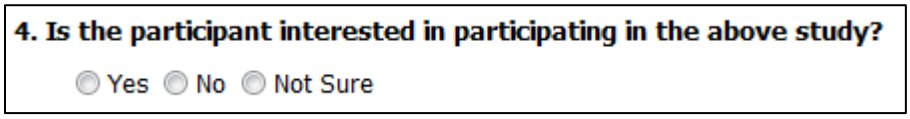
Once a participant has been asked to participate in this study please complete the Follow Up of Eligible Study Participant eCRF.

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.)*

Reasons	Level of importance for the participant declining the study		
Conflicting Responsibilities (Work, School, Family, etc.)	Very Important	Important	Somewhat Important
Time Commitment	Very Important	Important	Somewhat Important
Unable/Unwilling to Travel	Very Important	Important	Somewhat Important
Participant does not tolerate OGTT/IVGTT/MMTTs well	Very Important	Important	Somewhat Important
Fear of Study Drug Risks	Very Important	Important	Somewhat Important
Concerns about receiving placebo	Very Important	Important	Somewhat Important
Family wishes to wait until participant is older	Very Important	Important	Somewhat Important
Does not want to be blinded to individual test results during the study	Very Important	Important	Somewhat Important
Unwilling to take investigational drug	Very Important	Important	Somewhat Important
Pregnant, nursing or planning children in the future	Very Important	Important	Somewhat Important
Monetary Compensation	Very Important	Important	Somewhat Important
Refused; no reason given	Very Important	Important	Somewhat Important
Other			

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.

4.7 Eligibility Reports

To assist sites with identifying participants who are potentially eligible for the Oral Insulin Study, the TNCC has created an eligibility report that is updated daily. The report assists sites by listing participants who are at different stages of eligibility (i.e. mIAA+ only, mIAA++, all BAA criteria met and awaiting a normal OGTT, etc).

The report is located in each clinical center and affiliate Natural History/Pathway to Prevention report folder. Please refer to section 11.7 for details regarding how to access these reports.

A detailed training regarding how to navigate to and interpret the eligibility report can be accessed from the TN07 protocol page under the Working Documents portlet→Current Tools→Trainings. Please see section 11for additional information regarding this folder. A link to this training document is below:

04 TN07 Interpreting the List of Eligible TN07 Participants Report 01Nov12

5. VISIT PROCEDURES

The source documents for all visits are located on the members website in the TN07 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 TN07 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 of the instructions regarding preparation for an IVGTT	NA	NA
At Visit	Administer the screening consent and if applicable screening assent, and local HIPAA form.	Consent & Assent	OT01 Initial Visit
At Visit	Register the participant in the online system **Please Note:** ***This step can also occur during the Pre-visit time point if preference of site.*** **Please Note:** ***The PID registered should be the same PID in the TN01 Natural History/Pathway to Prevention Study.***	NA	Participant Registration
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.	Volunteer Understanding Assessment	NA
At Visit	Collect participant’s family and medical history	Complete Medical History	OT01 Initial Visit
At Visit	Ask the participant about what medications he/she is currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	ConMeds	Concomitant Medications

At Visit	Conduct a physical exam	Complete PE	OT01 Initial Visit
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	OT01 Initial Visit
At Visit	Conduct IVGTT	Local IVGTT Source	NA
At Visit	Screening lab collection: 1. IVGTT 2. Autoantibodies 3. Mechanistic Assessments (if applicable) a. PBMC/Plasma b. RNA	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. **Please Note:** ***Please send the initial IVGTT sample as a priority sample checking "priority" for each IVGTT sample in the online specimen collection form. Please review the TN07 Laboratory Manual of Operations and Specimen System User Manual for additional information about priority samples.***	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

*Depending upon site workflow, barcodes may be scanned prior to, during, or after the visit.

* For specific instructions on how to conduct an IVGTT please see appendix E.

5.2 IVGTT Results – TOSOH and RIA

Description: The determination of first phase insulin release (FPIR) for the Oral Insulin Study is based on the sum of the 1 and 3 minute RIA insulin values. However, there are two types of test to measure insulin in an IVGTT: TOSOH and RIA. TOSOH insulin results have a 5 business day turnaround time while RIA insulin results have a 16 business day turnaround. To

expedite the randomization process, the TNCC has created an algorithm in which TOSOH insulin results can be used to predict RIA insulin results for determining above and below threshold first phase insulin release (FPIR). FPIR is calculated by summing the 1 and 3 minute insulin results of an IVGTT.

Using this algorithm, for the initial IVGTT, if the sum of the 1 and 3 minute TOSOH insulin results are high enough, sites may proceed with randomizing participants based upon receipt of the TOSOH results because the TNCC is confident that RIA results for the IVGTT (when received) will indicate an above threshold result. Likewise, if the sum of the 1 and 3 minute TOSOH insulin results for the initial IVGTT are low enough, sites may proceed with completing a confirmatory IVGTT (completed during the baseline visit) because the TNCC is confident that RIA insulin results (when received) will be below threshold.

If TOSOH insulin results for the initial IVGTT fall within a certain range, they are considered "indeterminate" and RIA insulin results must be received before the site will know if the initial IVGTT is above or below threshold.

The final determination of the first phase insulin release being above or below threshold will remain based on RIA insulin results as per protocol.

5.3 Harmonized Assay Adoption and TN07 Eligibility

Description: In May 2010, TrialNet adopted use of the Harmonized Assay for GAD65 and ICA512. To maintain the integrity of the Oral Insulin Study, participants will continue to be eligible for the Oral Insulin Study based on the TrialNet Standard Assay only (for GAD65 and ICA512).

Harmonized Assay positive results for GAD65 and ICA512 do not count toward Oral Insulin eligibility.

5.4 Visit 0 Baseline:

Window: Randomize within:

1. *7 weeks (52 days) of a normal OGTT*
2. *6 months (210 days) of a confirmed positive mIAA (mIAA positive on at least 2 samples, one of which occurred within 210 days of randomization).*
3. *6 months (210 days) of having at least 1 other antibody present on 2 separate samples (one of which occurred within 210 days of randomization).*

Harmonized Assay positive results for GAD65 and ICA512 do not count toward Oral Insulin eligibility.

The Site will receive the Screening/Initial visit IVGTT results from the TNCC. If the screening IVGTT is **above threshold** then coordinator may proceed with the following baseline visit procedures. Please note, participants in this category do not need to be scheduled for an in-person baseline visit.

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review the participant's eligibility and verify that subject meets all eligibility criteria for this study. Ensure that the relevant autoantibody (210 day) and OGTT (52 days) windows have not lapsed. Please print out a copy of the participant's eligibility labs. PI needs to sign as source document. **Please note: *Contact the TNCC CRA to verify eligibility prior to randomization. Do not randomize a subject prior to confirming eligibility with the TNCC.*** If the OGTT window lapses while awaiting IVGTT results and the eligibility committee does not approve an extension, the participant must return for another OGTT to assess eligibility and if again eligible, must start over with an initial IVGTT.	NA	NA
At Visit	Complete the online OT02 Eligibility eCRF **Please Note: *Upon completion of the form, the status of the participant should indicate "eligible". If the participant's status reflects eligible, proceed to randomizing the participant. If not, please contact the TNCC.***	Eligibility Form	OT02 Eligibility
At visit	Randomize participant online. Within the Oral Insulin protocol homepage, select "Assign Treatment" **Please Note: *Make note of the randomization number in the source documents.***	NA	Assign Treatment
At Visit	Complete a Natural History/Pathway to Prevention NH07 Change of Status eCRF form to indicate the participant is now inactive in Natural History/Pathway to Prevention. The reason selected should be "Entry into a type 1 diabetes prevention study."	NA	NH07 Change of Status
At Visit	Order initial study drug kit through EMINENT by faxing/emailing the Agent Request Form to EMINENT (see Pharmacy Manual of Operations for additional information regarding ordering study drug). Indicate the participant's randomization number in the comments field of the Agent Request Form.	Agent Request Form	NA

Post Visit	Upon receipt of study drug kit from EMINENT, complete the Baseline OT14 Study Drug Dispensation and Return eCRF.	Study Drug Dispensation and Return	OT14 Study Drug Dispensation and Return
Post Visit	Call the participant to schedule receipt of study drug via courier.	Document correspondence	NA
Post Visit	Dispense study drug to participant via courier.	NA	NA
Post Visit	Call participant to ensure receipt and ask when the participant began taking study drug. Schedule the 3 month visit with the participant.	Document correspondence	NA
Post Visit	Record the date the participant began study drug on the online Treatment Start Date eCRF **Please Note:** ***If more than 4 weeks lapse from randomization to treatment start, this is a protocol deviation and an OT13 protocol deviation form must be completed.***	Treatment Start Date	Treatment Start Date
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

If the screening IVGTT is **below threshold** the participant will need to be scheduled for an IVGTT during the baseline visit. If the screening IVGTT is below threshold, the participant cannot be randomized until completion of the confirmatory IVGTT during the baseline visit.

Please Note: A participant can be randomized on the same day as the confirmatory IVGTT.

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review the participant's eligibility and verify that subject meets all eligibility criteria for this study. Ensure that the relevant autoantibody (210 day) and OGTT (52 days) windows have not lapsed. Please print out a copy of the participant's eligibility labs. PI needs to sign as source document. **Please Note:** ***Call or email the TNCC trial coordinator to verify eligibility prior to randomization. Do not randomize a subject***	NA	NA

	prior to confirming eligibility with the TNCC. If the OGTT window lapses while awaiting IVGTT results and the eligibility committee does not approve an extension, the participant must return for another OGTT to assess eligibility and if again eligible, must start over with an initial IVGTT.		
Pre-visit	Schedule the participant for a baseline visit. Remind the participant of the instructions regarding preparation for an IVGTT **Please Note:** ***When scheduling the baseline visit, coordinators should make sure the visit occurs within the applicable eligibility windows for randomization. Participants can be randomized on the same day as the confirmatory IVGTT (i.e. during the baseline visit).***	NA	NA
Pre-visit	Order any supplies needed for the repeat IVGTT through the online Fisher supply ordering system.	NA	NA
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, etc).	NA	NA
At Visit	Conduct IVGTT	Local IVGTT Source	NA
At Visit	Screening lab collection: 1. IVGTT	Signed and dated printout of specimen collection form	Screening Specimen Collection
At Visit	Complete the online OT02 Eligibility eCRF **Please Note:** ***Upon completion of the form, the status of the participant should indicate "eligible". If the participant's status reflects eligible, proceed to randomizing the participant. If not, please contact the TNCC.***	Eligibility Form	OT02 Eligibility
At visit	Randomize participant online. Within the Oral Insulin protocol homepage, select "Assign Treatment" **Please Note:** ***Make note of the randomization number in the source documents.***	NA	Assign Treatment
At Visit	Complete a Natural History/Pathway to	NA	NH07

	Prevention NH07 Change of Status eCRF form to indicate the participant is now inactive in Natural History/Pathway to Prevention. The reason selected should be "Entry into a type 1 diabetes prevention study."		Change of Status
At Visit	Order initial study drug kit through EMINENT by faxing/emailing the Agent Request Form to EMINENT(see Pharmacy Manual of Operations for additional information regarding ordering study drug). Indicate the participant's randomization number in the comments field of the Agent Request Form.	Agent Request Form	NA
Post Visit	Upon receipt of study drug kit from EMINENT, complete the Baseline OT14 Study Drug Dispensation and Return eCRF.	Study Drug Dispensation and Return	OT14 Study Drug Dispensation and Return
Post Visit	Call the participant to schedule receipt of study drug via courier.	Document correspondence	NA
Post Visit	Dispense study drug to participant via courier.	NA	NA
Post Visit	Call participant to ensure receipt and ask when the participant began taking study drug. Schedule the 3 month visit with the participant.	Document correspondence	NA
Post Visit	Record the date the participant began study drug on the online Treatment Start Date eCRF **Please Note:** ***If more than 4 weeks lapse from randomization to treatment start, this is a protocol deviation and an OT13 protocol deviation form must be completed.***	Treatment Start Date	Treatment Start Date
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	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

*Depending upon site workflow, barcodes may be scanned prior to, during, or after the visit.

Please Note: If the FPIR is above threshold on the second IVGTT, the participant is considered to be above threshold.

5.5 3 Month Visit:

Window: +/- 6 weeks

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Schedule the participant for the visit.	NA	NA
Pre-visit	Remind the participant to bring in all study drug bottles for the visit. **Please Note:** ***Study drug should NOT be dispensed at the 3 month visit but should be assessed for subject compliance. Subject compliance will be noted only on the source document at this visit.***	NA	NA
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc).	NA	NA
At Visit	Collect participant's interim medical history (changes since last visit)	Medical History	OT03 3-month Visit
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Conduct a limited physical exam	Limited PE	OT03 3-month Visit
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher). If Grade 1, PI needs to sign source document.	AE assessment	Adverse Events
At Visit	Assess Drug compliance with the subject and determine if they have missed any pills during this timeframe. **Please Note:** ***If a subject has missed any pills, counsel the subject on an action plan to increase compliance moving forward (Please reference the Site Instructions to Increase Pill Compliance for suggestions on ways to help subjects increase compliance). At this visit, your site should not have the subject return or dispense any study drug. Study drug will be returned/dispensed at the 6 month visit.***	Document correspondence	NA
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	OT03 3-month Visit
At Visit	Visit lab collection: 1. Autoantibodies	Signed and dated printout	Screening Specimen

	2. HbA1c 3. Mechanistic Assessments (if applicable) a. PBMC/Plasma b. RNA	of specimen collection form	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).	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

*Depending upon site workflow, barcodes may be scanned prior to, during, or after the visit.

5.6 Semi-Annual Visits (Months 6, 18, 30, 42, 54, 66… END)

Window: +/- 6 Weeks

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Schedule the participant for the visit.	NA	NA
Pre-visit	Remind the participant to bring in all study drug bottles for the visit.	NA	NA
Pre-visit	Once the study visit is scheduled, complete the Agent Request form and order the resupply study drug kit through EMINENT by faxing/emailing the Agent Request Form (see Pharmacy Manual of Operations for additional information regarding ordering study drug). Indicate the participant's randomization number in the comments field of the Agent Request Form. Please request the resupply study drug kit in advance of the participant's visit to allow sufficient time for the kit to arrive from EMINENT.	Agent Request Form	NA
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc).	NA	NA
At Visit	Collect participant's interim medical history (changes since last visit)	Medical History	OT04 6-month Visit
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications

At Visit	Conduct a limited physical exam	Limited PE	OT04 6-month Visit
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	Assess Drug compliance with the subject and determine if they have missed any pills during this timeframe. **Please Note:** ***If a subject has missed any pills, counsel the subject on an action plan to increase compliance moving forward (Please reference the Site Instructions to Increase Pill Compliance for suggestions on ways to help subjects increase compliance).***	Document correspondence	OT14- Study Drug Form
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	OT04 6-month Visit
At Visit	Visit lab collection: 1. Oral Glucose Tolerance Test (glucose, insulin, and c-peptide samples) 2. Autoantibodies 3. HbA1c 4. Mechanistic Assessments (if applicable) a. PBMC/Plasma b. RNA	Signed and dated printout of specimen collection form	Screening Specimen Collection
At Visit	Collect all empty, partially full, and full bottles of study drug that were dispensed at the previous study visit. Empty bottles should be destroyed on site per your local pharmacy procedures. Partially full and full bottles should be returned to EMINENT in batch shipments or may be destroyed on site per local SOP.	Pharmacy/Drug Log	NA
At Visit	Dispense the resupply study drug kit containing 7 bottles of study drug to the participant and complete the OT14 Study Drug Dispensation and Return eCRF.	Pharmacy/Drug Log	OT14- Study Drug Form
At Visit	Schedule the participant for an interim phone call in 3 calendar months.		NA
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit*	Scan barcodes for each central laboratory sample into the online specimen collection form(s).	NA	NA

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

*Depending upon site workflow, barcodes may be scanned prior to, during, or after the visit.

For Situations Where the Resupply Study Drug Kit Has Not Yet Arrived From EMINENT

If a participant comes in for their follow-up visit and the resupply kit has not yet arrived from EMINENT, your site should follow the below procedures:

Step 1. Once your site schedules the participant's follow-up visit, please complete the Agent Request Form and fax/email to EMINENT to order a resupply study drug kit.

Step 2. EMINENT will send the site a resupply kit for the participant containing 7 bottles of study drug.

Step 3. At the participant visit, if the kit has not yet arrived from EMINENT, your site should collect all 7 bottles of study drug that were dispensed at the participant's previous visit including empty, partially full and full bottles.

Step 4. The Trial Coordinator should re-dispense 1 full bottle of study drug to the participant in clinic.

Step 5. When the resupply kit arrives from EMINENT, your site should pull 1 full bottle out of the resupply study drug kit and destroy the bottle on site per your local protocol or return the bottle to EMINENT in your next batch shipment of study drug return.

Step 6. Your site should ship the resupply study drug kit containing 6 full bottles of study drug to the participant.

Step 7. Remember if this situation occurs to note all drug dispensed/returned in the SAME OT14 Study Drug eCRF even if bottles are dispensed on different dates.

a. Ex: The kit has not arrived in time for the subject's visit on December 1st and the subject returns 2 full bottles of study drug.
   i. Note 64 pills returned (2 full bottles- 32 pills in each bottle. 32+32=64 pills)
   ii. Re-dispense 1 full bottle (32 pills) at the visit to the subject. Document this event in the source.
b. On December 15th, the resupply kit arrives from EMINENT for the subject.

i. Remove 1 full bottle from kit and destroy on site per local SOP or return to EMINENT in next batch shipment.
ii. Mail remaining 6 bottles of study drug to the subject (192 pills).
iii. Subject will have a total of 224 pills dispensed for the visit (32+192=224 pills).
iv. Document this event in the source for the subject.

c. On Visit OT14 Study Drug eCRF, note 64 pills returned and 224 pills dispensed on the same eCRF (even though the dates of dispensation are different). Below is an image of how the OT14 eCRF should display.

d. Failure to document study drug in this manner will cause errors in pill compliance for the subject.

Please Note: This is the only situation where returned study drug may be re-dispensed to a participant. Also, a participant should never have more than 7 bottles of study drug in their possession at any time.

5.7 Interim Phone Calls (Months 9, 15, 21, 27, 33, 39. 45. 51. 57. 63. 69…END)

Window: +/- 6 weeks

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	This phone call should be scheduled 3 calendar months after each semi-annual and annual visit is completed.	NA	NA
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, etc).	NA	NA
At Visit	Collect participant's interim medical history (changes since last visit)	Medical History	OT06- 3-month Phone contact

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	Assess Drug compliance with the subject and determine if they have missed any pills during this timeframe.	Document correspondence	OT06- 3-month Phone contact
At Visit	Ask the participant about current pregnancy status	Document correspondence	OT06- 3-month Phone contact
At Visit	Schedule the participant's next follow up visit	NA	NA
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 Annual Visits (Months 12, 24, 36, 48, 60, 72… END):

Window: +/- 6 weeks

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Schedule the participant for the visit.	NA	NA
Pre-visit	Remind the participant to bring in all study drug bottles for the visit.	NA	NA
Pre-visit	Once the study visit is scheduled, complete the Agent Request form and order the resupply study drug kit through EMINENT by faxing/emailing the Agent Request Form (see Pharmacy Manual of Operations for additional information regarding ordering study drug). Indicate the participant's randomization number in the comments field of the Agent Request Form. Please request the resupply study drug kit in advance of the participant's visit to allow sufficient time for the kit to arrive from EMINENT.	Agent Request Form	NA
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc).	NA	NA

At Visit	Collect participant's interim medical history (changes since last visit)	Medical History	OT05 Annual-month Visit
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Conduct a physical exam including lifestyle assessments, height/weight, and abdominal circumference	PE and Lifestyle Questionnaire	OT05 Annual-month Visit
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	Assess Drug compliance with the subject and determine if they have missed any pills during this timeframe. **Please Note:** ***If a subject has missed any pills, counsel the subject on an action plan to increase compliance moving forward (Please reference the Site Instructions to Increase Pill Compliance for suggestions on ways to help subjects increase compliance).***	Document correspondence	OT14- Study Drug Form
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	OT05 Annual-month Visit
At Visit	Visit lab collection: 1. Oral Glucose Tolerance Test (glucose, insulin, and c-peptide samples) 2. Autoantibodies 3. HbA1c 4. Mechanistic Assessments (if applicable) a. PBMC/Plasma b. RNA	Signed and dated printout of specimen collection form	Screening Specimen Collection
At Visit	Collect all empty, partially full, and full bottles of study drug that were dispensed at the previous study visit. Empty bottles should be destroyed on site per your local pharmacy procedures. Partially full and full bottles should be returned to EMINENT in batch shipments or may be destroyed on site per local SOP.	Pharmacy/Drug Log	NA
At Visit	Dispense the resupply study drug kit containing 7 bottles of study drug to the participant and complete the OT14 Study Drug Dispensation and Return eCRF.	Pharmacy/Drug Log	OT14- Study Drug Form
At Visit	Schedule the participant for an interim phone call in 3 calendar months.		NA

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

*Depending upon site workflow, barcodes may be scanned prior to, during, or after the visit.

5.9 Description of Study Procedures

5.9.1 Volunteer Understanding Assessments

Definition: As part of the consent process, the participant will also be required to complete a short questionnaire Volunteer Understanding Assessment that is designed to ensure that the participant understands the study, as well as what is being asked of him/her. The purpose of the Volunteer Understanding Assessment is to enhance the consenting process.

Procedure:

Step 1. Give the survey to the participant following the description of the study but before the Informed Consent Form has been signed.

Step 2. If the participant is under the age of 18, the participant's parent/guardian will be required to complete the Volunteer Understanding Assessment independent from the participant.

Step 3. The site coordinator will review the completed Volunteer Understanding Assessment with the participant (and his/her parent/guardian in the case of an adolescent participant), taking special care to review any questions the participant answered incorrectly and answer any questions about the study. If any questions were missed, please document that the correct answers were reviewed with the participant (his/her parent/guardian) in the source documentation.

Step 4. Documentation regarding completion and review of the Volunteer Understanding Assessment should be kept in the participant's source documents.

5.9.2 Randomization/Treatment Assignment (Baseline)

Definition: Randomization is a method based on chance alone by which study participants are assigned to a treatment group.

Eligible study participants will be randomized by the TrialNet Coordinating Center through the online randomization process at the baseline visit and will be assigned a study randomization number corresponding to the treatment group assignment.

The participant will randomly be assigned to one of the following two groups:

- Active Oral Insulin
- Placebo

Participants will be randomized, in approximately equal numbers. The randomization method will be stratified by the major TrialNet study site. This approach ensures that study site will not be a potential confounder.

The Oral Insulin Trial is a double-masked trial, in that the participant, those involved in participant care at the sites, and the TNCC are masked to the participant's group assignment. The TrialNet Central Pharmacy and the TN statistician will know to which treatment group each participant is assigned. In the event that unmasking is required, contact the Oral Insulin Clinical Research Administrator at the TNCC.

The TrialNet Coordinating Center will generate a randomization schedule for the study sites. The Randomization Number will be a five-digit code in XX-XXX format where each study family's code is unique. The Randomization Number will in no way reflect the treatment group to which the participant has been assigned. If more than one member of a household or family is participating in the trial, only the first one randomized will have a unique randomization number. All subsequent household members will have the same randomization number.

5.9.3 Study Drug Return/Dispensation (Baseline, 3 Month, Semi-Annual and Annual Visits)

Definition: During each follow-up visit, the site will assess study medication compliance and dispense resupply study drug kits to the participant.

Participants will be instructed to take one capsule of study medication daily. All participants will receive 7 full bottles of study medication at each visit in a participant-specific kit. Each bottle contains 32 capsules so participants should be dispensed a total of 224 capsules at each visit.

Note: The number of capsules in the full un-opened study drug bottles should be included in the count of the number of capsules returned. Lost capsules and capsules left at home should also be included in the count of number of capsules returned.

Please refer to the Pharmacy Manual of Operations for additional study drug dispensation/return procedures and Appendix D for study drug information for the participant.

5.9.3.1. *Initial Study Drug Dispensation Procedure*

When a site is dispensing the first 7 bottles of study drug to the participant, the following procedures should be completed:

Procedure:

Step 1. Site coordinator will review study medication procedures with the participant during the baseline visit as well as over the phone when confirming receipt of the kit via courier.

Step 2. When participant is randomized, the site coordinator will complete an Agent Request Form and fax/email to EMINENT. Site coordinators should indicate the participant's randomization ID in the comments field of the Agent Request Form.

Step 3. EMINENT will send the coordinator a kit containing 7 bottles of study medication for the participant.

Note: International sites will receive shipments from and return bottles to a distribution vendor called Biotec, however the international sites will still correspond with EMINENT regarding sending forms and ordering/allocating study drug.

Step 4. Site coordinator will contact participant via phone to arrange for delivery of the study kit and complete the baseline OT14 Study Drug Form.

a. The "date study drug dispensed" should be the date the site shipped the drug via courier.
b. The coordinator should indicate that the participant received the study drug "by courier".
c. The relevant information from the bottles should be entered online for each bottle dispensed.
d. Each bottle contains a 3 part tear off label. One label should remain on the bottle. One tear off label should be affixed to the site's source documentation and the other tear off label discarded. Each bottle's label and the exterior of the study drug kit will contain the participant's randomization number.

Step 5. The coordinator should call the participant on the expected day of drug delivery to confirm receipt and review any questions the participant may have. The coordinator should ask the participant when he/she began treatment with the capsules and record the date on:

a. The "treatment start date" form in the online data capture system and
b. In the OT03 3 Month Follow-Up Visit Form, Section E, Question 1:" Record the date that the participant began taking the study drug"

5.9.3.2. ***Procedure for Study Drug Dispensation at Subsequent Follow-Up Visits***

Participants should be instructed to bring ALL study drug bottles (empty, full, and partially full bottles) to all follow-up visits. The study coordinator should dispense medication using the following procedures during follow-up visits:

Procedure:

Step 1. Once your site schedules the participant's follow-up visit, please complete the Agent Request Form and fax/email to EMINENT to order a resupply study drug kit.

Medication is ordered based on randomization number. Trial coordinators should request a resupply study drug kit on the *Agent Request Form* and write the participant's randomization number in the "Comments" field on the form.

Step 2. Once the participant arrives for their study visit, the site coordinator should collect all 7 bottles of study medication that were dispensed at the participant's previous visit.

a. Empty bottles should be discarded per site's standard operating procedure. If the site does not have an SOP then empty bottles may be returned to EMINENT for destruction on a quarterly basis.
b. Partially full and full bottles should be returned to EMINENT (International sites send to Biotec) on a quarterly basis (March, June, September, December) or may be destroyed on site per local procedures.
    i. The site coordinator should return all partially full bottles of study medication to EMINENT on a quarterly basis using the Agent Return Form (International Sites should returned partially full bottles to Biotec on a quarterly basis using the Agent Return Form).

Step 3. At the participant's visit, the site should dispense the resupply kit containing 7 full bottles of study drug to the participant.

a. Please reference the Pharmacy Manual of Operations for additional information regarding procedures with EMINENT and detailed information regarding study drug storage and dispensation.

Step 4. Site coordinator should complete an OT14 Study Drug form in the online data capture system.

a. For "number of study capsules returned" the coordinator should count the number of capsules from partially full bottles AND full bottles that were returned (32 capsules in each full bottle) and record the total number of capsules returned (include the number of pills left at home or lost in the total).
b. For "number of study capsules dispensed" the coordinator should always dispense a resupply kit to the participant containing 7 full bottles of study drug and therefore 224 capsules should be dispensed during each follow-up visit.
c. The coordinator should enter relevant information from the bottles dispensed in the online OT14 Study Drug Form.
d. Each NEW bottle contains a 3 part tear off label. One label should remain on the bottle. One tear off label should be affixed to the site's source documentation and the other tear off label discarded. Each bottle's label and the exterior of the study drug kit will contain the participant's randomization number

Please Note: For situations where the resupply study drug kit has not yet arrived from EMINENT, please refer to section 9.3.8.

5.9.4 AE (Adverse Event) Assessment (All visits except Initial)

Definitions:

Adverse event defined by TrialNet is "a*ny occurrence or worsening of an undesirable or unintended sign, symptom or disease whether or not associated with the treatment and study procedures."*

Serious Adverse Event: an adverse event associated with the treatment or study procedures that suggest a significant hazard, contraindication, side effect or precaution (as described below) is to be reported as a serious adverse event (SAE).

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

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

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

Reportable Adverse Event: defined per protocol. For TN07, only AE's determined to be CTCAE 3.0 grade 2 or greater are reportable and should be submitted to the TNCC using the online AE reporting system. Events related to the progression of disease (hyperglycemia, hypoglycemia, and diabetes onset) do not need to be reported as adverse event. ALL serious adverse events (regardless of grade or relatedness to disease progression) must be reported.

TrialNet Reporting Timeline:

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

  -OR-
  - Is Unexpected/Unanticipated
- All other (suspected) reportable AEs must be reported to TrialNet within **20 working days** of the notification of the event or of the site becoming aware of the event.

Procedure:

Step 1. Utilize source document as a guide.

Step 2. Ask participant if they have experienced any new or worsening symptoms since last visit- if yes, proceed to step 3

Step 3. Complete AE report in online system (if applicable).

Step 4. Fulfill any local site reporting requirements (to ethics board/IRB/etc).

Step 5. If AE is a serious adverse event which the medical monitor and/or investigator** judge as unexpected and possibly, probably or definitely related to study agent, the coordinator should complete FORM FDA3500A (MedWatch Report), submit to the FDA, and immediately fax/email to the TNCC.

***All events that are serious, unexpected, and possibly, probably, or definitely related to study drug based on Medical Monitor review require submission of a MedWatch report (even if the Medical Monitor's review differs from the investigator's assessment). Regardless, in the event

that the investigator feels compelled to submit a MedWatch report (even if, per the Medical Monitor's review, a MedWatch is not required) the investigator is free to do so.

5.9.5 Clinical Assessments

5.9.5.1. ***Screening Medical History (Initial or Baseline)***

Definition: Medical History is defined as an account of a patient's past and present state of health obtained from the patient or relatives.

Procedure:

Step 1. Utilize source document as a guide.

Step 2. Complete all sections of the source document (answer all questions).

Step 3. Enter data from source document into the online eCRF (all applicable fields).

5.9.5.2. ***Interim Medical History (All Visits beyond Initial or Baseline Visit)***

Definition: Review the participant's health during the study and document any changes to the participant's medical history.

Procedure:

Step 1. Utilize source document as a guide.

Step 2. Complete all sections of the source document (answer all questions).

Step 3. Enter data from source document into the online eCRF (all applicable fields).

5.9.5.3. ***Physical Exam Including Lifestyle Assessments (Initial and Annual Visits (Month 12, 24, 36, 48, 60, 72…END))***

Definition: Physical Exam is the process by which a health care provider investigates the body of a patient for signs of disease.

Procedure:

Step 1. Utilize source document as a guide

Step 2. Collect the following physical assessments:

a. Seated arm blood pressure: Record the systolic and diastolic arm pressure while the participant is seated
b. Weight: Record the participant's weight as either kilograms or pounds. It is not necessary to provide both units. Shoes should routinely be removed when taking this assessment.
c. Height: Record the participant's height as either centimeters or inches. It is not necessary to provide both units. Shoes should routinely be removed when taking this assessment. Participants less than 18 years of age should have their height assessed using a stadiometer, if available.
d. Abdominal Circumference: Abdominal circumference should be measured using a spring-loaded tape measure (tape measures available for ordering on the

TrialNet Supply Ordering System). Follow the procedures listed below. Record abdominal circumference to the nearest .1 cm or .01 inch.

i. **To take measurements:** Pull an appropriate amount of tape out of the housing. Wrap the tape once around the waist (see instructions below). Align the tape's "zero line" alongside of the tape graduations. Use the Metric units (cm). Now simply pull on the end of the tensioning mechanism until the **calibration point** is just seen. Read the measurement next to the tape's "zero line".

ii. **What is meant by "calibration point":** When you pull slightly harder and harder on the tensioning device, two colored beads will be seen separated by a silver disk. When you are pulling with exactly four ounces of force, you will see a silver disk separating the two beads. When you see one of the two beads, you are at the "calibration point". Remember, four ounces is not a great deal of force, in fact, it is approximately equal to the force required to lift a stack of 20 U.S. quarters. So don't pull so hard that the beads start to disappear into the end cap of the tensioning device; that is too much force.

iii. Ideally, waist circumference would be measured in the morning after voiding and before breakfast. If this is not possible, efforts should be made to measure each subject under conditions as similar as possible on all visits (e.g., same time of day, fasting, limited consumption of fluids).

iv. Participants should stand with feet together. The measure should be taken around the abdomen horizontally at midpoint between highest point of the iliac crest and lowest part of the costal margin in the mid-axillary line.

v. Mark the midpoint on both sides using a washable marker. (Participant may be asked to assist in passing the tape around the abdomen by holding the end of the tape in position). The tape should be aligned with the markings and positioned in the horizontal plane at the correct height. At this point, it may be helpful to mark the position of the tape on the participant's back in order to insure proper placement for the second reading. The measurer may also want to utilize a mirror or a second measurer to assist with making sure the tape is lined up horizontally. (If the tape cannot be made horizontal across the waist markings, default to the right hip.) The participant should be asked to keep relaxed arms at the sides and to breathe naturally. Ask the participant to breathe in and out, and then to hold his/her breath at the end of a normal exhalation. Record circumference to the nearest 0.1 centimeter. Remove the tape and repeat the procedure.

vi. If the second abdominal circumference measurement is within .5cm/0.2in of the first measurement, record the first measurement. If the second abdominal circumference differs by more than 0.5 cm/0.2 in, a third reading should be taken. The third reading should be documented as long as it comes within 0.5 cm of either the first or second measurement.

e. Review Systems: Record whether the following systems are reported as normal or abnormal by the participant and normal or abnormal upon examination. If either the participant or the clinical indicated an abnormality for any of the systems, explain the abnormality.

i. Head, Ears, Eyes, Nose, Throat (HEENT)

ii. Neck

iii. Thyroid

iv. Lungs
v. Chest/Breasts
vi. Heart/Circulatory
vii. Abdomen
viii. Musculoskeletal
ix. Neurologic
x. Genitourinary/Testes
xi. Skin/Nails
xii. Lymph Nodes
xiii. Other (Please note any other clinical findings from the physical exam).

f. For subjects less than 18 years of age, indicate the participant's sexual development using the Tanner Scale and record whether the participant is in Stage 1, Stage 2, or Stage 3 or greater for breast (female), genitalia (male) and pubic hair (both). Note that Tanner Staging is completed for participants onceTanner Stage 3 is reached. See Appendix H or the Tanner Stage descriptions.

Step 3. Complete all sections of the source document (answer all questions)

Step 4. Complete Lifestyle Questionnaire Assessment and mail to TNCC at the below address: (Please batch Questionnaires and ship quarterly)

Lifestyle Questionnaires
TrialNet Coordinating Center
USF Health Informatics Institute

3650 Spectrum Blvd, Ste 100
Tampa, FL 33612

Step 5. Enter data from source document into the online eCRF (all applicable fields).

5.9.5.4. ***Limited Physical Exam (Month 3 and Semi-Annual Visits (Month 6, 18, 30, 42, 54, 66…END))***

Definition: Physical Exam is the process by which a health care provider investigates the body of a patient for signs of disease. Patients will undergo a limited physical exam during month 3 and semi-annual visits.

Procedure:

Step 1. Utilize source document as a guide.
Step 2. Collect the following physical assessments. The participant should rest for 5 minutes before these assessments are performed:
a. Seated Blood Pressure
b. Height
c. Weight
d. Abdominal Circumference (not done at month 3)

Step 3. Complete all sections of the source document (answer all questions).

5.9.5.5. ***Concomitant Medications (All visits)***

Definition: Used to collect all medications that the participant is taking before and during the study. After screening visit, only changes in concomitant medications need to be captured on source documents and the eCRF.

Procedure:

Step 1. Utilize source document as a guide.

Step 2. Complete all sections of the source document (answer all questions).

Step 3. Enter data from source document into the online eCRF (all applicable fields).

5.9.6 Pregnancy Monitoring (All visits excluding Baseline Visit)

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.

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 or IVGTT if the participant is confirmed pregnant).

a. Instruct the participant to return all study medication bottles (empty, partially full, and full unopened bottles) to the site. The site should then discard empty bottles per local SOP and return all full and partially full bottles to EMINENT quarterly (or to Biotec if the site is an International site). Refer to the Pharmacy Manual of Operations for detailed instructions regarding return of study drug.

Step 3. Ask the participant if they would be willing to be followed on the study to record information about their pregnancy outcome. Study coordinators should also instruct participant that monitoring of diabetes risk and pregnancy should be continued by her OB/GYN because she will not be monitored by the Oral Insulin study site while pregnant.

a. If the participant does not want to be followed, withdraws consent, or becomes lost to follow up complete the “Change in Status” form.
b. If the participant agrees to be followed:
    i. At the end of the pregnancy, document the pregnancy outcome on the “OT11 - 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 IVGTT’s or OGTT’s.

Step 4. Complete an OT07 Change in Study Drug eCRF in the online data capture system and indicate the participant is discontinuing study drug because of pregnancy.

Step 5. 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 6. Complete an OT12 Change of Status PRN eCRF in the online data capture system
   a. The reason for withdrawal would be "pregnancy."

Step 7. Complete the "OT10 Pregnancy Confirmation" e-CRF PRN form.
   a. If the participant is willing to continue with future follow-up visits after the pregnancy please indicate this in question 5, "Is the participant willing to continue with future follow-up visits?"

Step 8. Fulfill any local reporting requirements (IRB, GCRC, etc.).

Please Note: Participants are not eligible for study visits while pregnant.

Participants are eligible to continue with study visits 3 months after the outcome of the pregnancy. Although they are able to resume study visits for sample collections 3 months after pregnancy outcome, participants are not eligible to continue taking study drug until they have stopped breastfeeding. If a participant who was previously pregnant would like to return for continued follow-up the site would complete an OT12 Change of Status eCRF to reactivate the participant and continue following the participant based on the participant's original visit schedule.

Participants who have been previously pregnant are eligible to continue study drug when they are no longer breastfeeding. If a participant decides to continue the use of study drug, when the participant stops breastfeeding and resumes taking study drug, the site would complete an OT07 Change of Study Drug eCRF and indicate the participant is re-starting study drug.

5.10 Withdrawal from Study Medication

A participant may be discontinued from study medication due to adverse effects of treatment that in the judgment of the investigator are related to the study medication or participants may voluntarily withdraw from study medication. Please note, a participant who is withdrawn from study medication should still continue to be followed on the Oral Insulin Study and continue with follow-up visits as outlined above. If a participant is withdrawn from study medication the site should follow these procedures:

Step 1. Complete the "OT07 Change of Study Drug" PRN eCRF in the online electronic data capture system and indicate that study medication has been discontinued.
   a. The "Date of Visit" should be the date the coordinator determined the participant is no longer taking study drug.
   b. The "Date change in study drug status effective" should reflect the date the subject was discontinued from taking study medication.
   c. Indicate the reason the participant discontinued study drug.

Step 2. If participant agrees to continue with study visits the site should continue with follow-up visits and assessments as scheduled.

Step 3. If the participant no longer wants to participate in the study, please follow procedure outlined in section 5.12.3.1.

5.11 End of Study Participation

5.11.1 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.

5.11.2 Participant Randomized in Error

If it is determined that a participant has been randomized and he/she was not eligible for the study, please contact your TNCC coordinator immediately for further guidance.

5.11.3 Lost to Follow-Up and Withdrawal from Study Medication

This study utilizes an intent-to-treat design in which all subjects randomized into the study should continue all scheduled follow-up assessments until the time of onset of diabetes, death, or the declared end of the study. Participants who are withdrawn from study medication will continue to be followed on the Oral Insulin protocol. Participants who are lost to follow-up may return to the Oral Insulin study at any point if they have not met study endpoint (Development of Type 1 Diabetes). Noncompliance with taking study medication or missing study visits does not eliminate participants from the trial.

5.11.4 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 follow these procedures:

Step 1. Complete the OT12 “Change of Status” PRN eCRF (See section 9.9 for instructions on how to access PRN forms) in the online electronic data capture system and indicate that the subject has withdrawn/lost to follow up and is inactive.

a. The “Date of Visit” should be the date the coordinator determined the participant is inactive and that a change of status should occur.
b. The “Date change in status became effective” should reflect the date the subject withdrew or the date it was determined the participant was lost to follow up.
c. Proceed to section B, enter a date of withdrawal if appropriate and indicate the primary reason for withdrawal (lost to follow-up or withdrawn consent).
d. No further eCRF’s or visits will be expected in the system for the subject when the participant is inactive based on the most recent change of status form.

Step 2. If a participant changes to inactive status and discontinues taking the study drug the site should also complete the OT07 “Change of Study Drug” eCRF PRN in the online electronic data capture system and indicate that study medication has been discontinued.

a. The “Date of Visit” should be the date the coordinator determined the participant is no longer taking study drug.
b. The “Date change in study drug status effective” should reflect the date the subject discontinued taking study medication.
c. If the participant withdrew consent or is lost to follow-up, the reason for study drug discontinuation would be “self-discontinued by participant”

Step 3. Complete the OT14 “Study Drug” eCRF PRN form in the online electronic data capture system and indicate the number of pills returned. Please refer to section 9.3.8 to review instructions for completing the OT14 Study Drug eCRF.

5.11.5 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”

5.11.6 Reactivation into the Study

A participant who has been inactive (lost to follow-up or withdrawn consent) may decide to resume active participation in the study. If the participant desires to return to the clinic for future follow-up visits, he/she should be allowed and encouraged to do so, regardless of the duration of the inactive period. If an inactive participant decides to reactivate the following procedures should be followed:

1. Complete an OT12 “Change of Status” PRN eCRF in the online electronic data capture system and indicate that the participant is being reactivated.
    a. The “Date of Visit” should be the date of the participant’s first visit after rejoining the study.
    b. The “Date change in status became effective” should reflect the date it was determined that the subject rejoined the study.
    c. Proceed to section C, enter the date of the subject’s first visit rejoining the study.
    d. The subject will rejoin the study according to the time point at which he/she would currently be due if the subject had remained on the study (based on date of randomization). For example, if a participant left the study at month 6 and decided to return 12 months later, the next expected visit – and therefore procedures to follow- would be the 18 month visit.
2. If the participant decides to continue study drug, then the site should complete the OT07 “Change of Study Drug” PRN eCRF in the online electronic data capture system and indicate that the participant is re-starting study medication.
    a. The “Date of Visit” should be the date of the participant’s first visit after rejoining the study.
    b. The “Date change in study drug status effective” would be the date the participant re-started study medication.
    c. Please note, question 3 (Reason the study drug was stopped) does not need to be completed and can be left blank when a participant is re-starting study medication. This section is only completed when a participant discontinues study medication.

5.11.7 Permanent Study Discontinuation (Medication and Follow-Up)

Once randomized, participants will continue to be eligible for follow-up in the Oral Insulin study until the time of onset of diabetes, death, or the declared end of study. If any of these three situations occur, a participant will be permanently withdrawn from study, including follow-up and study medication, and will not be eligible to return for future visits.

5.11.7.1. *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 (11.1mmol/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 1.75g/kg body weight to a maximum of 75g 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 Oral Insulin Study and will be asked to return for the next follow-up visit.

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).

Procedures:

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

1. Complete the OT12 “Change of Status” eCRF PRN in the online electronic data capture system and indicate that the subject has developed Type 1 Diabetes and is inactive.
    a. The “Date change in status became effective” should reflect the date the participant was diagnosed with type 1 diabetes.
    b. Proceed to section B, enter a date of withdrawal and indicate the primary reason for withdrawal (development of T1D)
2. Complete the OT07 “Change of Study Drug” eCRF PRN in the online electronic data capture system and indicate that study medication has been discontinued.
    a. The reason would be “development of T1D”

3. Complete the OT16 “Diabetes Onset Form” in the online electronic data capture system and indicate that the participant has developed Diabetes
4. Collect all study drug from participant and destroy all empty bottles on site per local SOP and return all full and partially full bottles to EMINENT quarterly (International sites return study drug to Biotec).
    a. Please refer to the Pharmacy Manual of Operations for additional information regarding study drug returns.
    b. Complete the OT14 “Study Drug” eCRF PRN form in the online electronic data capture system and indicate the number of pills returned. Please refer to section 9.3.8 to review instructions for completing the OT14 Study Drug eCRF.

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/Biochem 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/Biochem 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), the results of tests and/or the test procedures will be provided to the TrialNet Coordinating Center for review and adjudication by the Eligibility Committee (EEC)

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: Have the subject return for a repeat OGTT at a TrialNet Clinical Center or Affiliate Site as soon as possible for a full OGTT or a reduced OGTT (including fasting and 120 minute samples at minimum). If the subject is diagnosed prior to coming in for a repeat OGTT, collect as much information regarding symptoms at onset including date insulin therapy began and contact the TNCC to review the diagnosis criteria to see if the subject should be reviewed by the Diabetes Adjudication Committee/Eligibility Committee.

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 Diabetes Adjudication/Eligibility Committee).

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.

Scenario 5:

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

The Oral Insulin 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.

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 TrialNet Diabetes Adjudication/Eligibility Committee.

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 9.9.4 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 OT07, OT14, and OT16 forms and collect study drug from participants). Coordinators should contact the TNCC Clinical Research Administrator if they have any questions.

5.11.7.2. *Declared End of Study*

When the study is declared to be over, the site should follow these procedures for participants enrolled at the site:

1. Schedule participant for an end of study visit. Contact the TNCC for further instructions regarding end of study visits.
2. Complete an OT12 Change of Status Form in the online data capture system indicating the participant is becoming inactive.
    a. The reason would be "Maximum follow-up reached"
3. Complete an OT07 Change in Study Drug form in the online data capture system indicating the participant is discontinuing study medication.
    a. The reason would be "Study discontinuation"

5.11.7.3. ***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 “OT09 - Mortality Event Form” in the online data capture system. Complete this form regardless of the cause of death.
3. Complete a “OT12 - Change in Study Status” Form in the online data capture system indicating the participant is becoming inactive.
4. Complete a “OT07 - 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.

5.12 Missed Visits/Visits Occurring Outside Window

5.12.1 Missed Visit

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

1. For that visit time point, under “Tracking” select “Not Done” for all forms and indicate the reason the visit was not completed within the allowable window.
2. Complete one Protocol Deviation form indicating that the visit was missed
3. Document the reason for the missed visit in the source.

5.12.2 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.

5.12.3 Missed or Incomplete Specimen Collections

When scheduling sample collections during visits, Study Coordinators should keep in mind the prioritization of samples.

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

Step 1. If the missed sample is used to determine study endpoint (such as an OGTT), the participant should be scheduled to return for the procedure as soon as possible.

Step 2. If the missed sample is not used to determine study endpoint (i.e. autoantibodies, HbA1c, RNA, and PBMC) the study coordinators should attempt to reschedule the participant. Although strongly encouraged, rescheduling these types of missed collections is not as imperative as rescheduling study endpoint collections.

Step 3. Completion of forms:

a. If the participant returns for the collection and it occurs within the allowable visit window for that visit then the site should
    i. Collect the specimen using the collection form listed under that visit in the participant details page (and not a PRN form, also no protocol deviation).
b. If the participant returns for the collection and it occurs outside of the allowable visits window, the site should:
    i. Collect the specimen using a PRN form,
    ii. In the specimen collection form for the actual visit, indicate “not collected” for the missed sample, and
    iii. Complete a protocol deviation eCRF in the online data capture system indicating “Protocol-specified assay collection schedule not followed.”
c. If the participant does not return for the collection at all, then the Study Coordinator should:
    i. In the specimen collection form for the actual visits, indicate “not collected” for each sample missed during the scheduled visit.
    ii. Complete a protocol deviation eCRF in the online data capture system indicating “Protocol-specified assay collection schedule not followed.”

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. This can be done by navigating to the member directory and searching for sites by zip code or city. You may also go to the "Site Locator" under "Network Sites and Activities on the main TrialNet Homepage

The Site Locator will tell you what TrialNet studies sites are approved for.

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.

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. Once the consent form is signed at the new site, the originating site can complete the online OT17 Participant Site Transfer Form and officially transfer the participant's information to the new site.

Step 6. The originating site will notify the new site when participant has been transferred in the online system.

Step 7. If this is a permanent transfer, the TNCC will ensure EMINENT has been informed of the participant's permanent transfer. Failure to notify the TNCC of a subject transfer will result in a delay in receiving study drug at the new site.

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, including specimen collections, can be performed at an unapproved site. .

7. Informed Consent

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

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

7.1 Required Elements of Informed Consent

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Applies only to protocols approved after March 12, 2012:

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

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

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

7.1.1 Assent of Children

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

7.1.2 Consent for Stored Samples

Participants are **not** required to provide consent for stored samples in order to participate in the Oral Insulin Trial. Participants also have the right to withdraw their consent to store samples at any time and to have their stored samples destroyed to the extent possible. The Consent Form contains 3 options for the participant:
I give permission to have my blood stored:

1. Yes, store all samples, including genetic samples: This checkbox gives the participant the choice of providing blood samples for storage that could be used to learn more about what causes diabetes, how to identify people at risk of diabetes, and its complications. Even if the participant decides not to have blood samples stored, he/she can still participate in this study.

2. Yes, store all samples, but not the genetic samples: This checkbox gives the participant the choice of providing some, but not all, of the blood samples for storage. If a participant chooses this option, the RNA samples will not be collected. Even if the participant decides not to have blood samples stored, he/she can still participate in this study.
3. No, I do not give permission to have any samples stored: This checkbox indicates that the participant does not want to have any samples collected for storage.

Purpose: At the Oral Insulin Trial Initial and Follow-up Visits, samples may be drawn for future studies to evaluate immune function and genetics. The samples will include: residual serum from autoantibody testing (drawn at all sites) and the following mechanistic samples only drawn at participating TrialNet sites: plasma for the evaluation of islet autoantibody epitope, affinity, isotyping and proteomics based on assessment of immune responses, PBMC for the evaluation of immune cell function, especially antigen-specific responses relevant to the hypothesis that oral insulin can induce a state of tolerance to islet proteins. Whole blood RNA will be tested for immune cell frequency and function by gene expression analysis. The total blood draw volume in adults is no more than 10.5 mL/kg or 500 mL in an eight week period, whichever is smaller. For children, no more than 5 mL/kg will be drawn at any single visit and no more than 9.5 mL/kg over an eight week period.

If a participant gave permission on the Informed Consent Form to have blood drawn for storage, the first of these samples will be drawn at the Initial Visit. On the Consent Form there are three choices for the participant:

1. **Yes, Store all samples including genetic samples**
2. **Yes, Store samples except genetic samples (RNA will not be stored)**
3. **No, do not store any samples**

By choosing **option 1**, the participant gave permission for the following samples to be drawn and stored:

- Autoantibodies including residual serum (All Sites)
- RNA (Mechanistic Collecting Sites Only)
- Plasma – PBMC (Mechanistic Collecting Sites Only)

By choosing **option 2,** the participant gave permission to store residual autoantibody serum and plasma only. RNA will not be drawn or stored.

By choosing **option 3,** the participant did not consent to have any samples stored. Therefore no mechanistic samples will be collected and the lab will automatically be notified to destroy any residual serum after autoantibody testing.

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

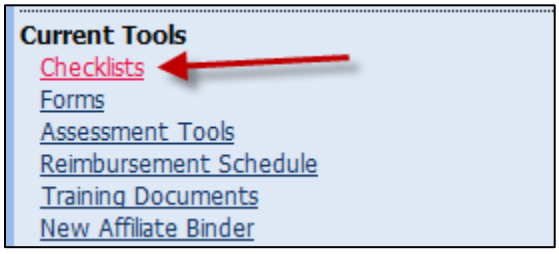
7.2.2 Documentation of the Informed Consent Process

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 TN07 protocol home page under "Checklists":



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.

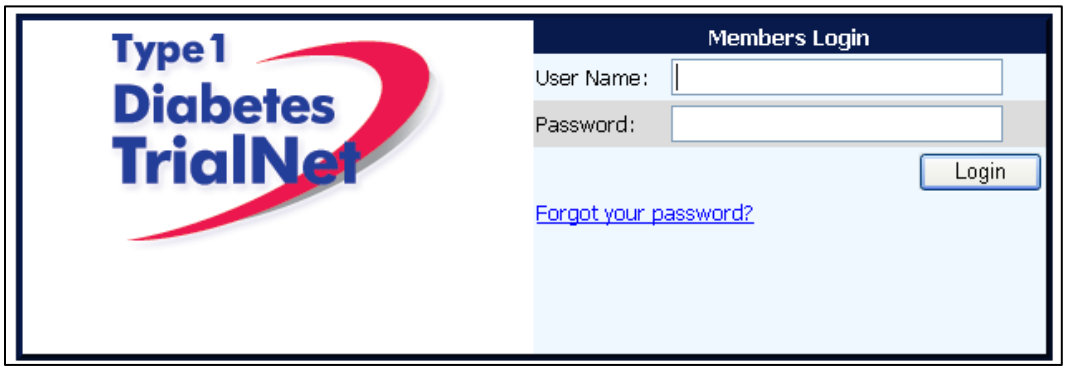
9. Online Data Capture System

9.1 Overview and Basic Functionality

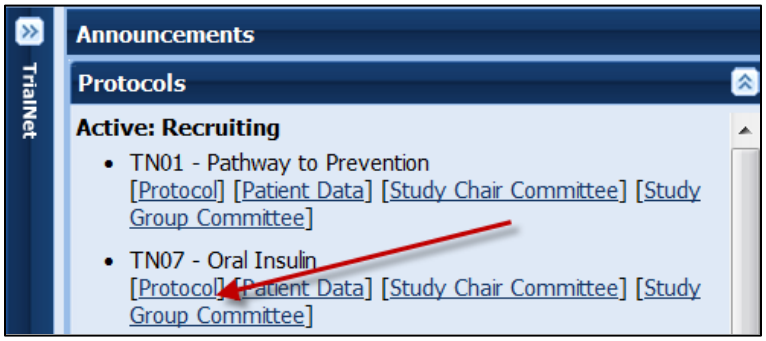
9.1.1 Login/Navigate to the TN07 Protocol Manager Area

Step 1. Procedure to login and navigate to the TN07 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.



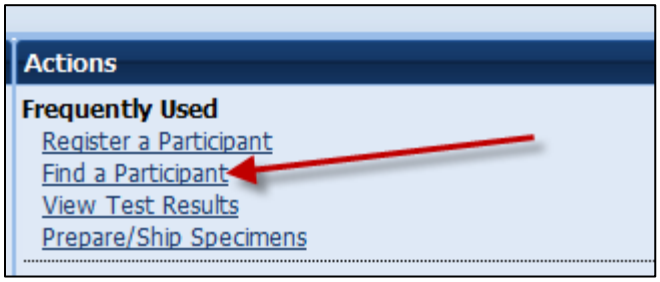
Step 3. Navigate to the “Protocols” portlet. Under TN07, select “Protocol.”



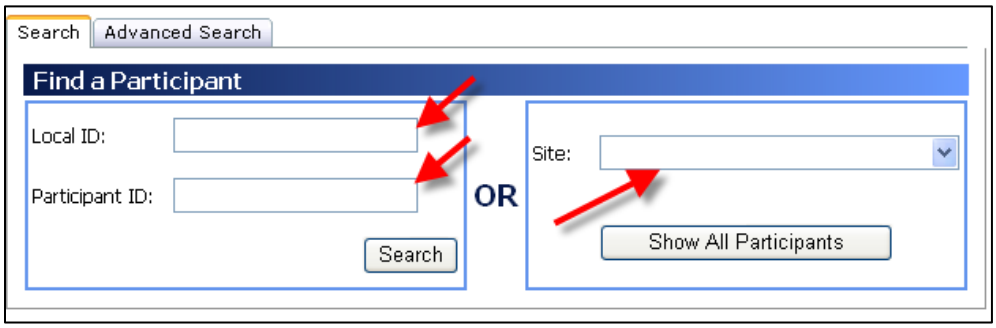
9.1.2 Finding a Participant

Note: This procedure will be done for every visit.

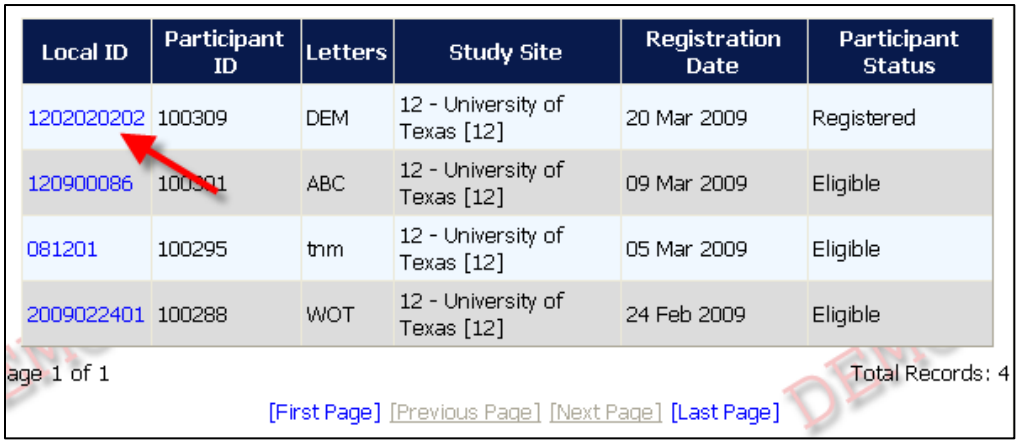
Step 1. Procedure to find participant: Once in TN07 Protocol, navigate to the "Actions" portlet and select "Find Participant."



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



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



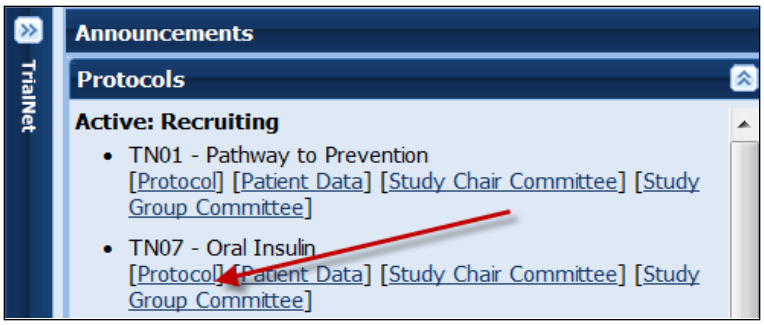
Local ID	Participant ID	Letters	Study Site	Registration Date	Participant Status
1202020202	100309	DEM	12 - University of Texas [12]	20 Mar 2009	Registered
120900086	100301	ABC	12 - University of Texas [12]	09 Mar 2009	Eligible
081201	100295	tnm	12 - University of Texas [12]	05 Mar 2009	Eligible
2009022401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

age 1 of 1 Total Records: 4

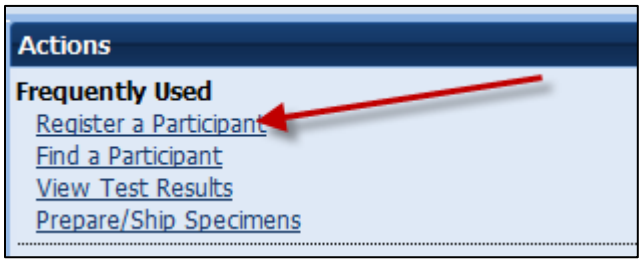
[First Page] [Previous Page] [Next Page] [Last Page]

9.1.3 Registering a Participant

Step 1. Log into TrialNet Members Website and navigate to the Protocols portlet. Select the "Protocol" link under TN07 – Oral Insulin:



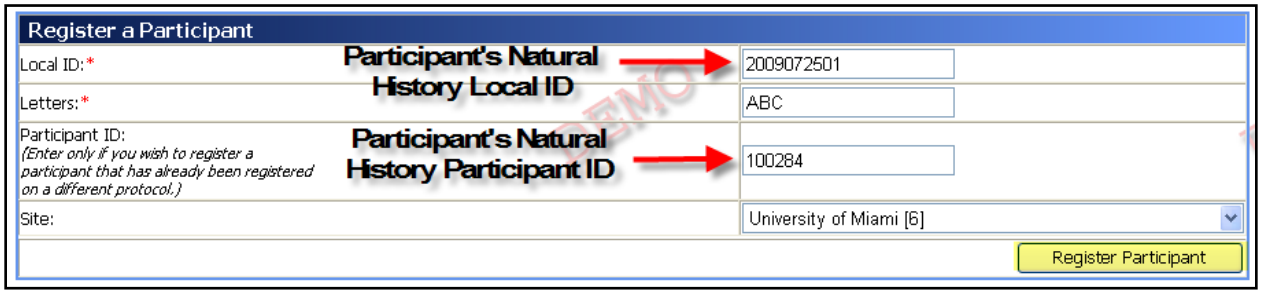
Step 2. Once in TN07 Home Page, navigate to the Actions portlet and select "Register Participant."



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

a. Local ID: Sites can enter the same local ID the participant has from the Natural History/Pathway to Prevention Study or if the Oral Insulin site is a different site than the Natural History/Pathway to Prevention site, a new local ID should be created and entered by the site. This can include numbers and letters.
b. Letters: Enter three letters.
c. Participant ID: Enter the **Same Participant ID** that the participant has already been assigned in the Natural History/Pathway to Prevention Study.
Site: Select applicable site.

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

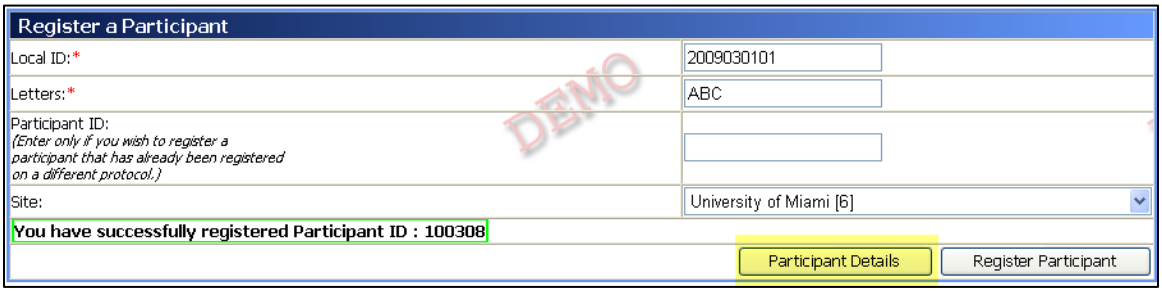


The Oral Insulin study recruits from the Natural History/Pathway to Prevention Study. Therefore all participants should already have a participant ID assigned to them. In the example above a participant from the Natural History/Pathway to Prevention Study is eligible for Oral Insulin. The participant already has a local ID of 2009072501 and participant ID of 100284.

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

Please Note: This should be the **SAME** participant ID that the participant already has been assigned from the Natural History/Pathway to Prevention Study. **If a new participant ID is accidentally created immediately contact the TNCC.**

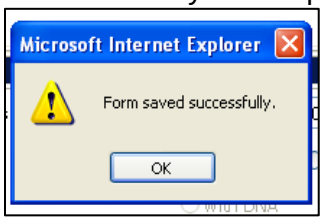
Step 6. If you want to view the participant details for the newly registered subject, select the "Participant Details" button at the bottom of the "Register a Participant" box.



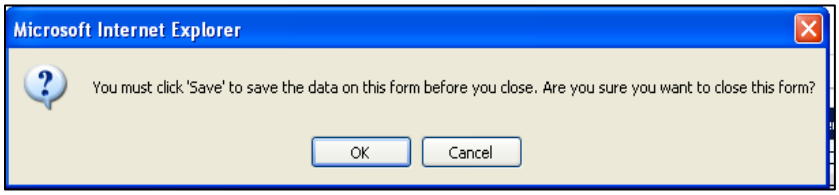
9.1.4 Save and Close e-CRFs

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

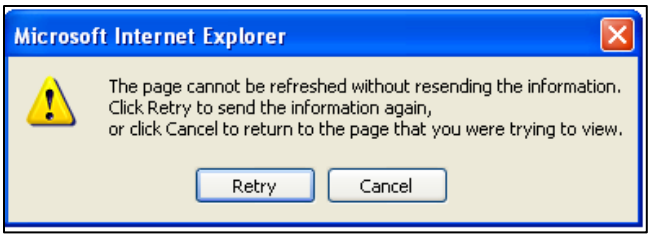
Step 1. Procedure to save and close-out form: After entering the data select "Save". The message "Forms saved successfully" will display.



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

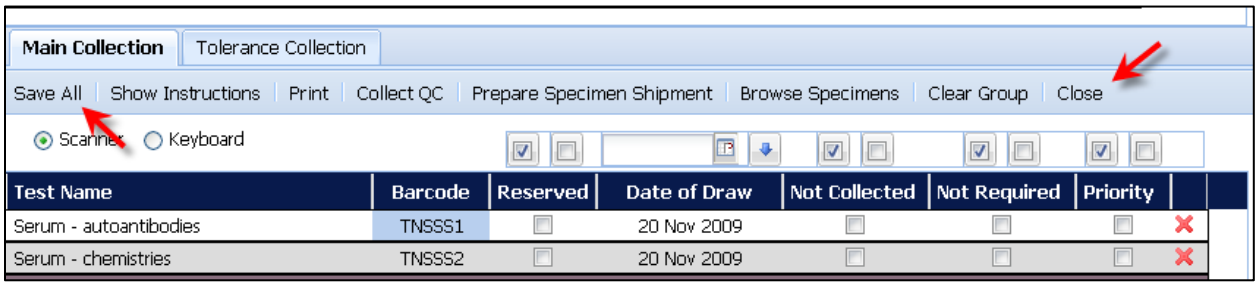


9.1.5 Save and Close Specimen Collection Forms

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.

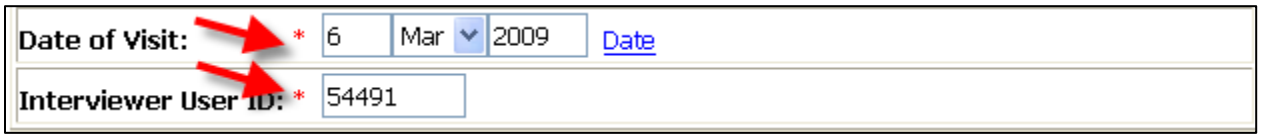


Please review the TrialNet Specimen Management System User Manual for potential error messages you may receive when attempting to save a collection form and additional information regarding collection forms.

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.

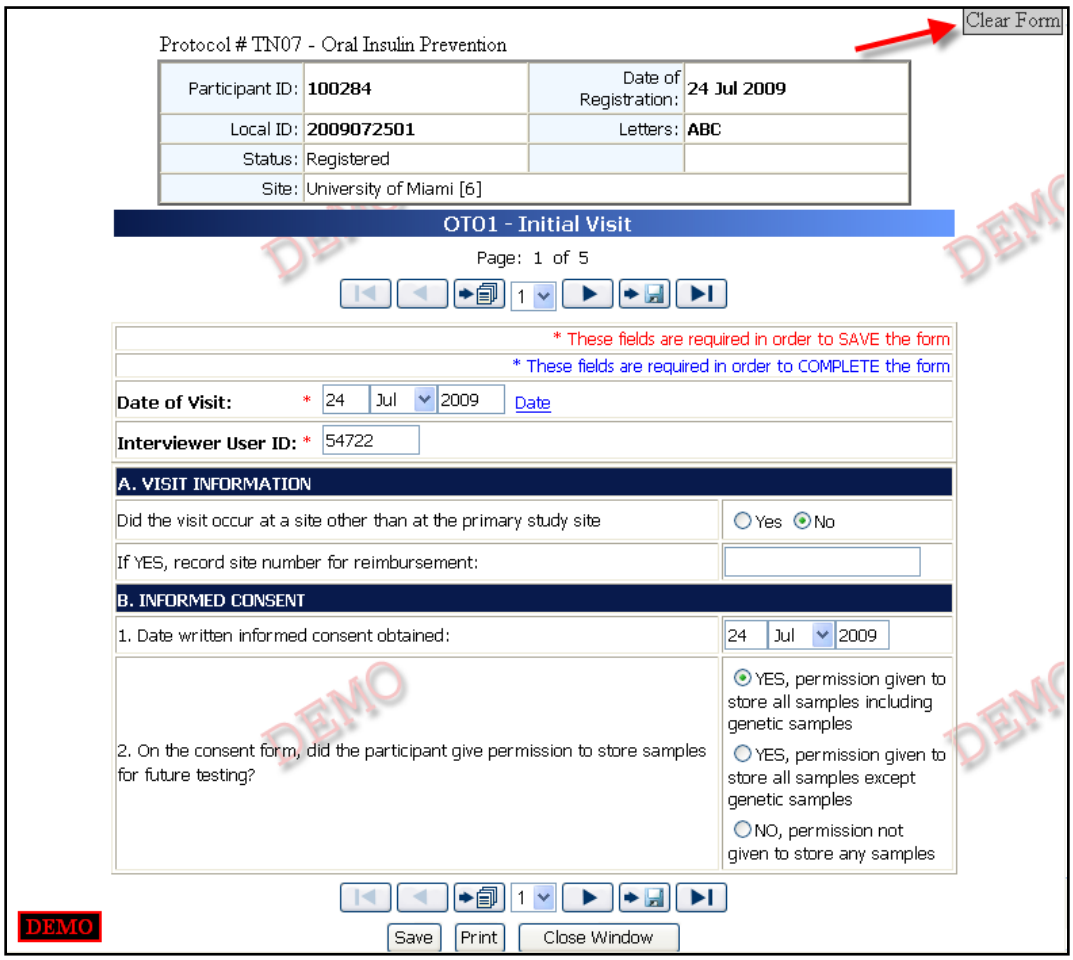
A description of this requirement is at the top of very form:

9.1.7 Clear ALL Data from a Form

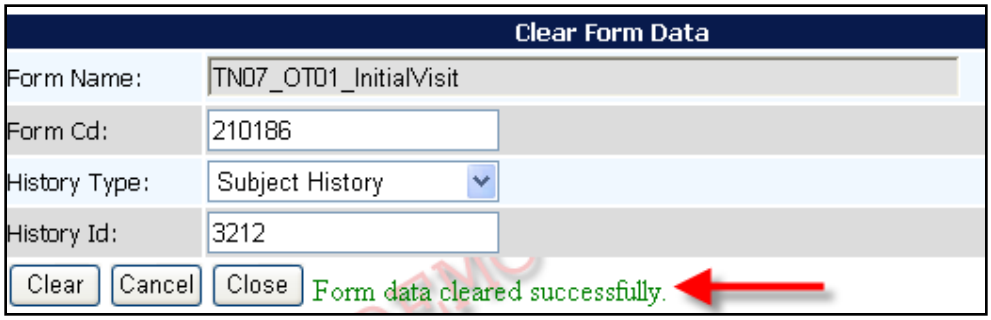
If you find you have mistakenly entered wrong data on a form, you can clear all data on the form as long as you are the person who entered the data on the form (determined based on the Interviewer user ID entered in the form).

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

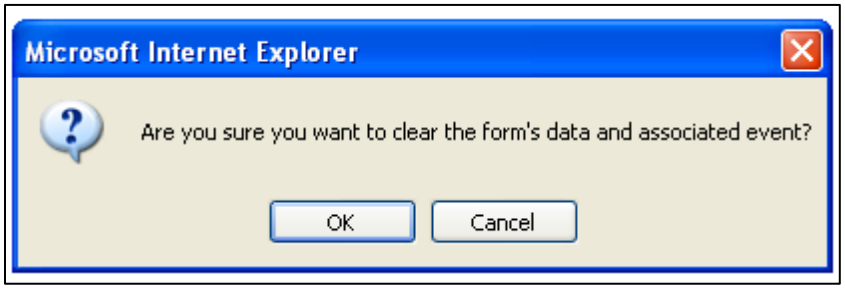
Step 2. Click on the button entitled “Clear Form” in the upper right hand corner of the screen.



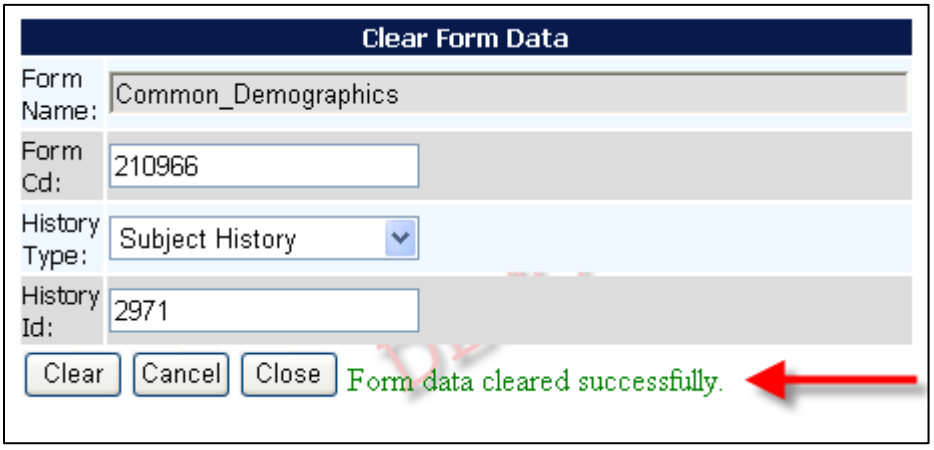
Step 3. The page will navigate to a description of the form you are about the clear (Clear Form Data box). If you are certain you wish to clear out all data on the form, click the button “Clear.”



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

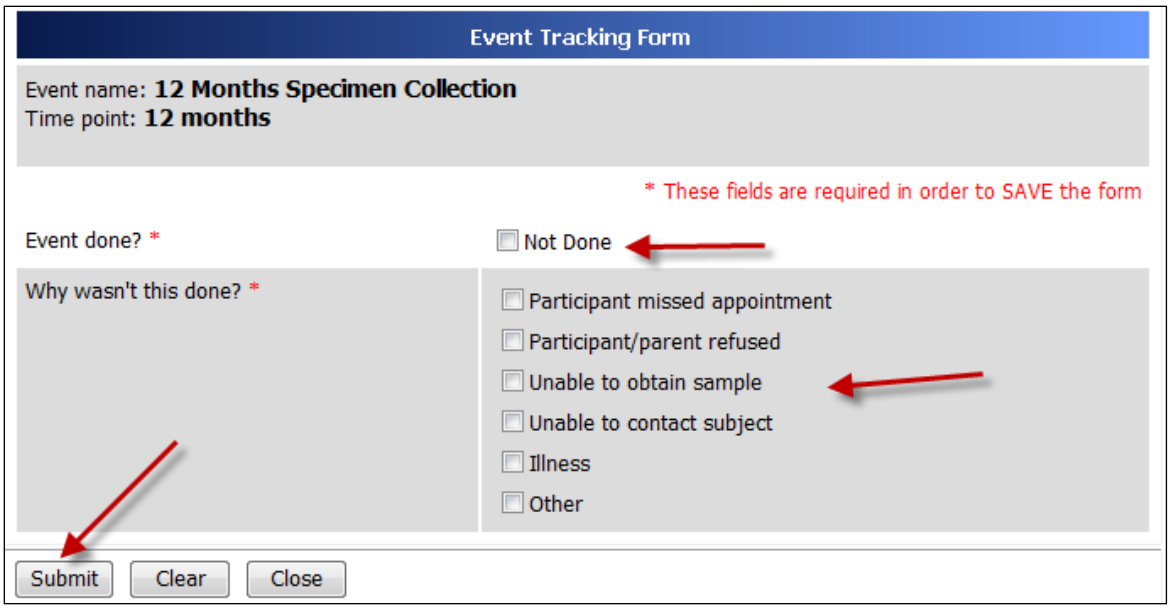
For instructions on how to clear data from a Collection Form please refer to the Specimen Management System User Manual

9.2 Participant Details

The Participant Details Screen provides, by participant, a list of all events generally required to be completed once the participant is registered on the study. The forms present at each visit follow the Schedule of Events/Assessments from the protocol.

Timepoint	Event Title	Tracking	Target Date	Event Status
Screening	OT01 - Initial Visit		03 Jan 2013	Complete
	Screening Specimen Collection		03 Jan 2013	Complete
	Concomitant Medications		03 Jan 2013	Complete
Baseline	Registration Form		03 Jan 2013	Complete
	OT02 - Eligibility		03 Jan 2013	Complete
	Treatment Start Date		03 Jan 2013	Complete
	OT14 - Study Drug Form		03 Jan 2013	Complete
3 months	OT03 - 3-month Visit		03 Apr 2013	Complete
	OT14 - Study Drug Form		03 Apr 2013	Complete
	Concomitant Medications			Complete
	3 Months Specimen Collection		03 Apr 2013	Complete
6 months	OT04 - 6-month Visit	Tracking	03 Jul 2013	
	OT14 - Study Drug Form	Tracking	03 Jul 2013	

- 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 or is completed outside of the allowable visit window.



- Target Date – When the event should occur according to the Schedule of Events from the protocol.
- 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.

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

If the answer to any questions is "no" or "zero", please enter this information in the form (i.e. if the form asks the number of study drug pill missed and the answer is zero, please indicate "0" in the applicable field).

9.3 Visit Forms

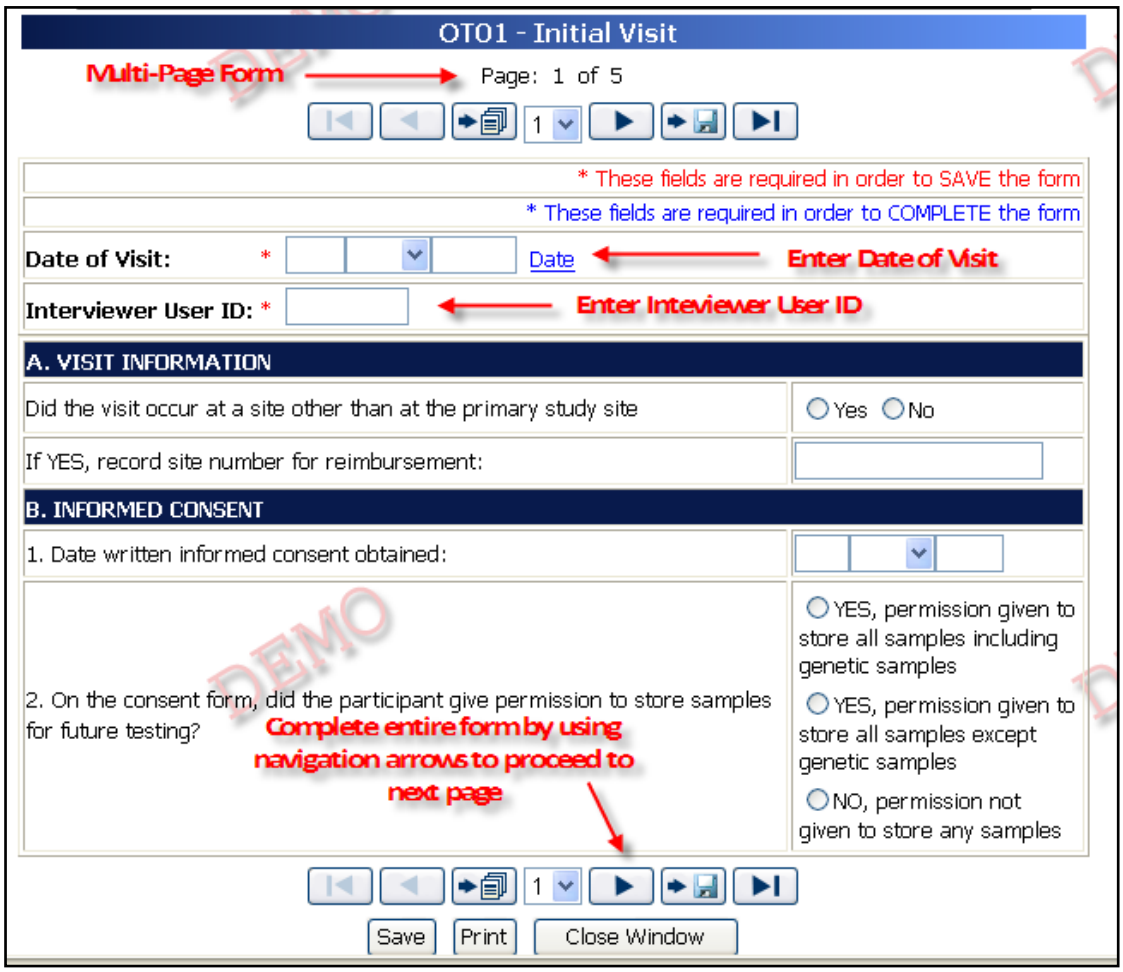
9.3.1 Data Entry for OT01 Initial Visit Form

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

Step 2. Under Event Title select OT01 Initial Visit.

Timepoint	Event Title	Tracking	Target Date	Event Status
Screening	OT01 - Initial Visit	Tracking	24 Jul 2009	

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



Step 4. Complete all sections of the form. Please note this is a 5 page form. Use the navigation arrows located at the bottom of the form to navigate to the next page.

a. Visit Information
    i. Date of Visit: The date the visit occurred
b. Informed Consent
    i. Date written informed consent obtained: Record the date that the participant signed the Informed Consent Form.
    ii. On the consent form, did the participant give permission to store samples for future testing: Select the bubble corresponding to the response the participant gave on the informed consent form:
        1. YES, permission was given to store all samples including genetic samples. If this option is chosen all mechanistic samples will be collected (at participating sites).
        2. YES, permission was given to store all samples except genetic samples. If this option is chosen, RNA will not be collected but all other mechanistic samples will be collected (at participating sites).
        3. NO, permission not given to store any samples. If this option is chosen, none of the mechanistic samples will be collected and labs will be notified to destroy residual samples.

c. Family History
    i. Have any of your first or second degree relatives been diagnosed with type 1 diabetes since the completion of the Natural History Family History Form (NH01F): This question collects information on whether the participant has any other first or second degree relatives that have been diagnosed with type 1 diabetes since the completion of the Natural History Family History Form (NH01F). **The relative(s) that was entered on the Natural History Form (NH01F) should not be entered on the OT01 form.** Select either **Yes** or **No** for this question and complete the table below for any NEW relatives that were diagnosed with diabetes since completion of the NH01F.
d. Medical History
e. Pregnancy Monitoring (If participant is male, proceed to section F).
f. Concomitant Medications (Past or Current Usage)
    i. This section gathers information regarding the participant's past or current medication usage. Some medications are not indicated for participation in the Oral Insulin Trial and if the participant has a history of taking them or is currently taking them he/she will not be eligible for the trial. However, if the participant begins taking the medications once he/she is randomized into the trial they will be monitored but the participant will not be forced to discontinue the trial.
        1. Immunosuppressives or immunomodulatories are agents or therapies to aid the body's immune system.
        2. K-sparing diuretics are agents that promote the secretion of urine through their effects on kidney function and deplete the levels of potassium in the process. Beta blockers are a class of drugs that block the action of adrenaline (a beta adrenergic substance) and can relieve stress to the heart muscle. Beta blockers are often used to slow the heart rate or lower the blood pressure. Niacin should only be considered if the participant is taking a prescription-strength supplement. Niacin ingested from diet or over the counter vitamins will generally not be in amounts high enough to affect tests.

Please Note: Trial Coordinators should stop and review the medication exclusion criteria from the Oral Insulin Trial protocol. If the participant answered YES to questions 1-3, make sure enough information is gathered to determine eligibility based on the criteria listed in the protocol. For example, if the participant answered Yes to question 1: have you taken in the past or are you currently taking immunosuppressive or steroid drugs, Coordinators need to determine whether the use has been within the past 2 years and at least 3 months in duration (from Exclusion Criteria #5 in the protocol).

g. General Physical exam
h. Specimens Drawn and Procedures Performed

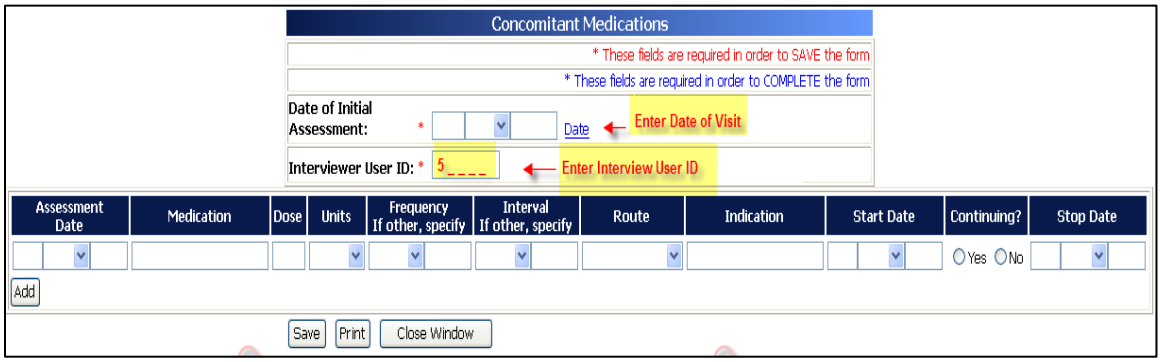
Step 5. After entering data, please reference section 9.1.4 Save and Close e-CRF form.

Please Note: Data should be entered for all forms within 30 days of the visit.

9.3.2 Concomitant Medications

The concomitant medications form is a running log of the participant's medication use throughout the study. Once completed during screening, the form will auto-populate for all subsequent visits. Any data entered on the form during a visit will populate in the next concomitant medications form. If a participant begins a medication and later stops it, then the site should go to the medication on the form where it was originally entered and change the response to questions "Continuing" to "no" and enter a stop date for the particular medication.

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.

Please Note: For additional information, please refer to the Concomitant Medications training document posted on the TrialNet TN07 Oral Insulin Protocol Page in the Working Documents portlet→Current Tools→Training Documents folder.
09 TN07 Concomitant Medications Log Instructions 20090827

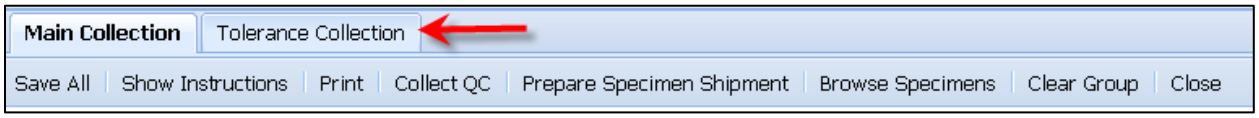
9.3.3 Specimen Collection Form: Main Collections

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 and IVGTTs.

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



Step 1. After completing the Main Collections navigate to the "Tolerance Collection" by selecting the "Tolerance Collection" tab.

Step 2. Please refer to the TrialNet Specimen Management System User Manual for additional information regarding completion of Specimen Collection forms.

9.3.5 OT02 - Eligibility Form

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

Step 1. Be sure the Source Document is completed prior to completing this specimen collection form.

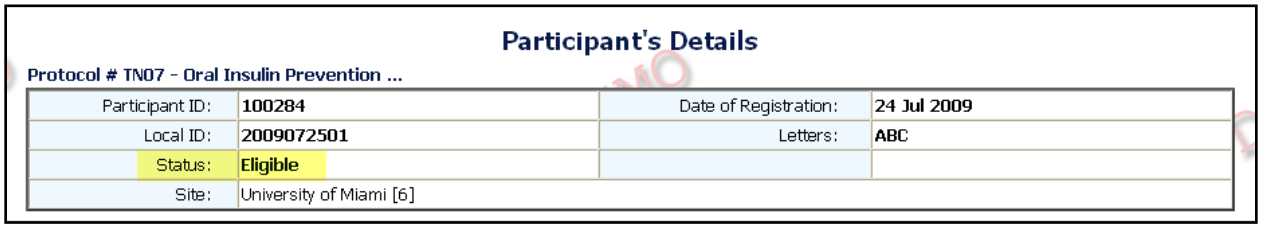
a. To document autoantibody, OGTT/IVGTT and HLA eligibility criteria, it is recommended to print a copy of the subject's "View Test Results" record and sign/date the print-out for inclusion in the subject's record.

Step 2. Under the Event Title – Select OT01 – Eligibility. When the form displays, enter Date of Visit and your Interview User ID.

Step 3. Complete all pages of the form.

Please Note: Leave Eligibility Committee Review question BLANK if the participant was not reviewed by the TrialNet Eligibility Committee

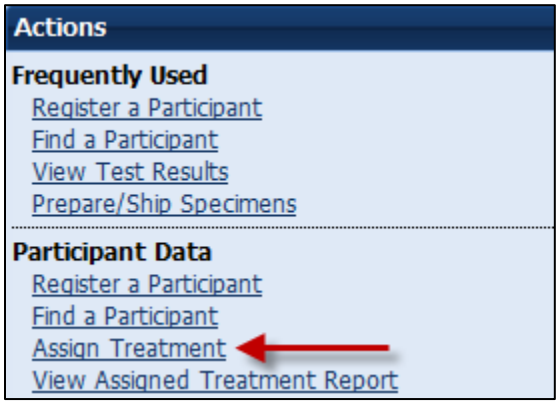
Step 4. After saving the completed form check the Participant Details screen to see if status of participant changed from Registered to Eligible.



9.3.6 Randomizing Participant/Treatment Assignment

Step 1. The ***OT02 Eligibility form must be complete*** and the subject must be eligible prior to assigning treatment to the subject. ***Please confirm subject eligibility with the TNCC TN07 Protocol CRA prior to randomizing any subject in the system.***

Step 2. Under the Actions portlet on the main TN07 protocol page select "Assign Treatment"

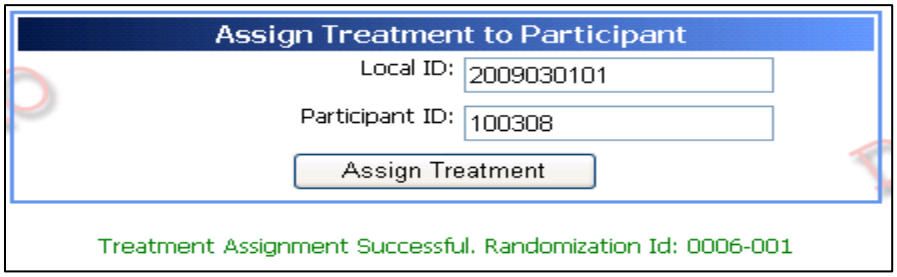


Step 3. A box will open titled Assign Treatment to Participant; enter both the Local ID and Participant ID. Select the box next to the question "Is a sibling already enrolled and assigned a treatment" only if the participant has a sibling already enrolled in the study.

If a sibling is already enrolled, then select this box and enter the sibling's participant ID in the space provided. Leave the box blank if it does not apply.

Step 4. Select Assign Treatment.

Step 5. 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 6. Make note of the randomization number in the source documents.

Step 7. Contact EMINENT using the Agent Request Form to request an initial kit of study medication for the participant. Please refer to the Pharmacy MOO for additional details regarding initial study drug ordering.

9.3.7 Treatment Start Date

After calling the participant to confirm receipt of study medication, please also ask for the date the participant began consuming study treatment. Enter this date in the treatment start date eCRF.

Step 1. Under the Event Title select: Treatment Start Date

Step 2. When the form displays, enter Date of Visit and your Interviewer User ID

Step 3. Enter the date the participant began treatment.

Step 4. After entering data Save and Close eCRF

Please Note: Once the OT02 Eligibility form is complete, the participant is randomized, and the treatment start date has been entered, subsequent visit forms will populate beyond the baseline visit for the participant.

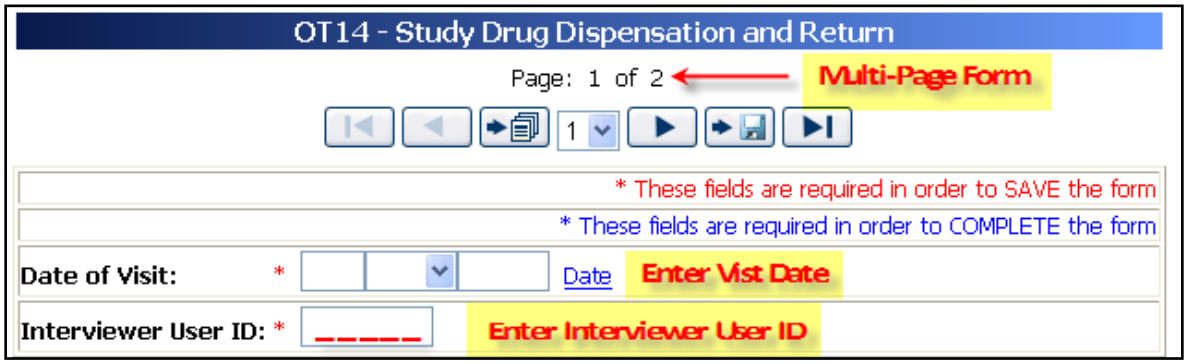
9.3.8 OT14 – Study Drug Form

This form should be completed any time study medication is returned or dispensed. The following procedures will be the same for each time an OT14 form is completed.

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

Step 2. Under Event Title - Select OT14 – Study Drug Form

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



Step 4. Complete all following sections on BOTH pages of this form:

i. Section B: Accounting of Study Drug
   1. *Note:* The total number of capsules returned should include a sum of the following:
      a. the number of capsules in partially full bottles
      b. The number of capsules in full unopened bottles that are returned
      c. The number of capsules lost
      d. The number of capsules forgotten at home

ii. Section C: Dispensation of Study Drug
   1. *Note:* The total number of capsules dispensed should include a sum of the following:
      a. The number of capsules in the newly dispensed study drug kit of 7 full unopened bottles.

Please Note: Participants should leave each visit with 7 full bottles of study drug which is 224 capsules total (32 capsules in each bottle).

iii. Bottle label information - Found on tear off label of the bottle.
   1. Bottle Number: The number bottle that has been dispensed to the participant (1, 2, 3, 4, etc.)
   2. Date bottle Dispensed
   3. Randomization #
   4. Package Lot #

iv. Section D: Additional Information

Step 5. Please Remember to ONLY complete One OT14 Study Drug Form per subject visit (even if drug is dispensed/returned on separate dates). This may occur if drug is left at home (and later mailed back by the subject to your site) or the resupply kit has not yet arrived from EMINENT in time for the subjects visit. If drug was left at home and is returned at a later date (via mail courier or at the next visit), the date entered into the OT14 Study Drug form should be the date the participant stopped taking drug from the old kit.

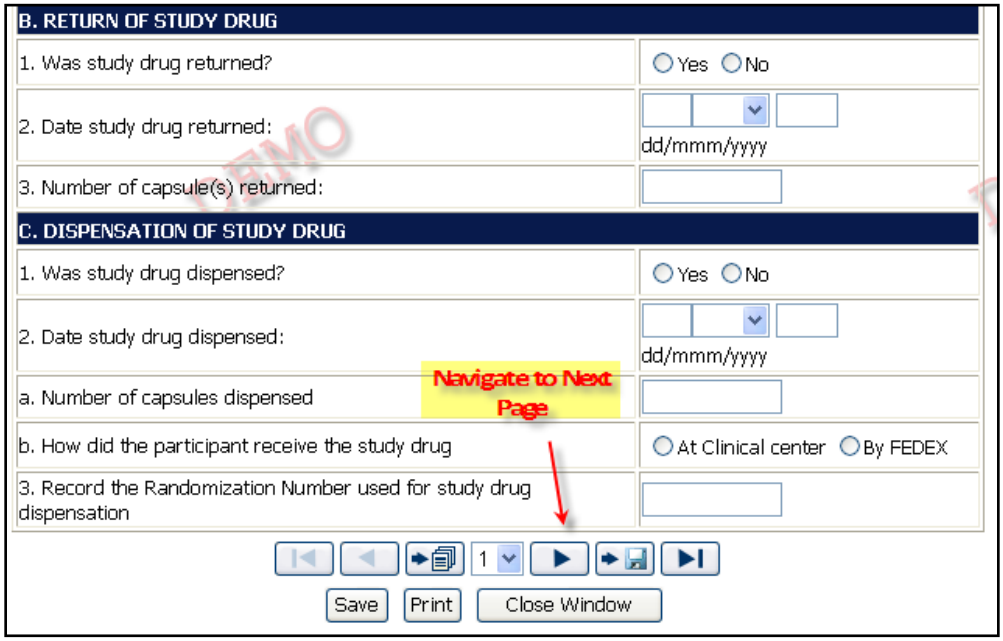
a. Ex: The kit has not arrived in time for the subject's visit on December 1st and the subject returns 2 full bottles of study drug.
    i. Note 64 pills returned (2 full bottles- 32 pills in each bottle. 32+32=64 pills)
    ii. Re-dispense 1 full bottle (32 pills) at the visit to the subject. Document this event in the source.
b. On December 15th, the resupply kit arrives from EMINENT for the subject.
    i. Remove 1 full bottle from kit and destroy on site per local SOP or return to EMINENT in next batch shipment.
    ii. Mail remaining 6 bottles of study drug to the subject (192 pills).
    iii. Subject will have a total of 224 pills dispensed for the visit (32+192=224 pills).
    iv. Document this event in the source for the subject.
c. On Visit OT14 Study Drug eCRF, note 64 pills returned and 224 pills dispensed on the same eCRF (even though the dates of dispensation are different). Below is an image of how the OT14 eCRF should display.

d. Failure to document study drug in this manner will cause errors in pill compliance for the subject.

Please contact the TNCC Protocol CRA for additional questions on the completion of the OT14 form.

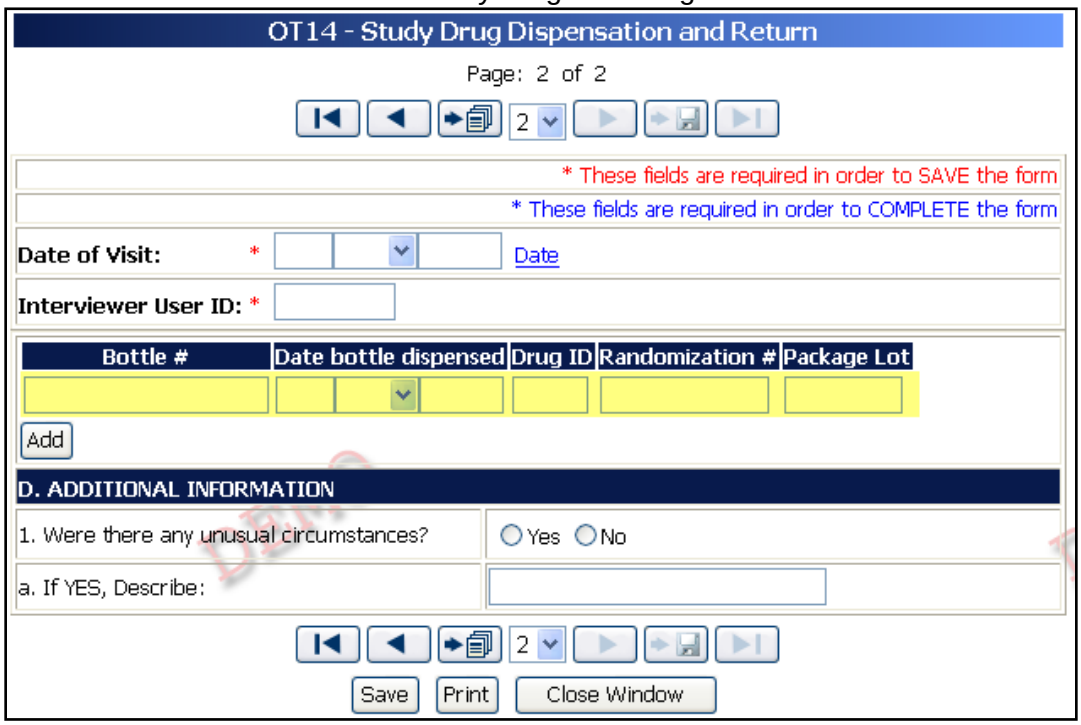
Please refer to the Pharmacy Manual of Operations for additional information regarding the accounting of study drug.

OT14 Study Drug Form Page 1:



Note: This is a two page form. Make sure both pages are completed by using the navigation arrows at the bottom of the page.

OT14 Study Drug Form Page 2:

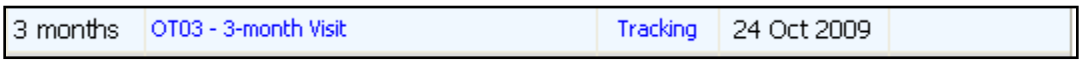


Note: Entering the bottle information is not a required field of the form and may be omitted to decrease the amount of data entry sites are required to complete. However, this information should be contained in source documentation.

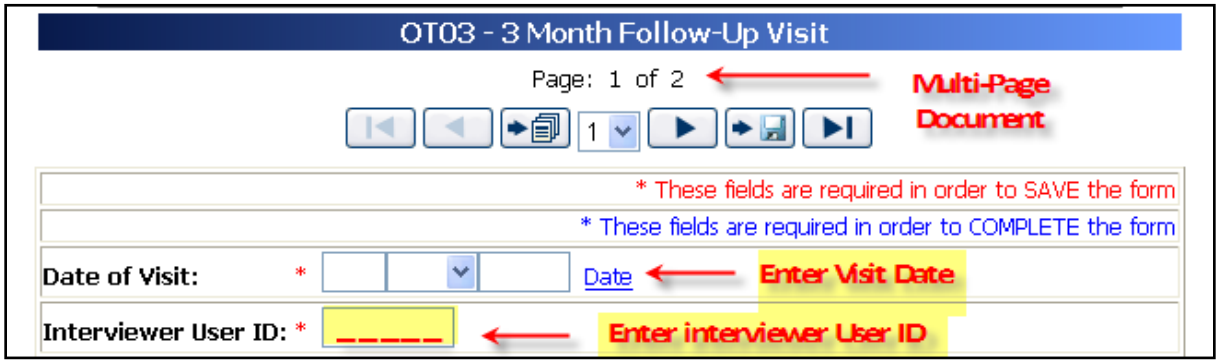
9.3.9 OT03 – 3 Month Visit Form

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

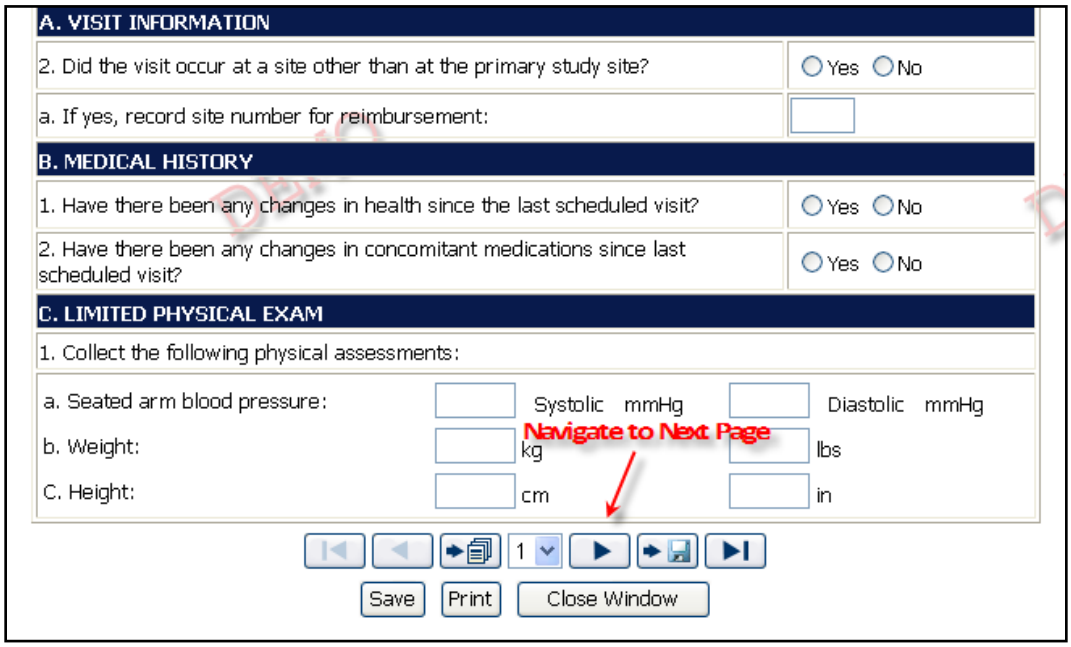
Step 2. Under Event Title - Select OT03 - 3 Month Visit



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



Step 4. Complete all sections for this form.



Note: This is a two page form. Make sure both pages are completed by using the navigation arrows at the bottom of the page.

Step 5. After entering data, Save and Close eCRF form.

9.3.10 OT04 – 6 Month Visit Form

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

Step 2. Under Event Title - Select OT04 - 6 Month Visit

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

Step 4. Complete all sections for this form.

Note: This is a two page form. Make sure both pages are completed by using the navigation arrows at the bottom of the page.

Step 5. After entering data, Save and Close eCRF form

9.3.11 OT06 – 3 Month Phone Contact Form

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

Step 2. Under Event Title - Select OT06 – 3 Month Phone Contact

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

Step 4. Complete all following sections for this form:

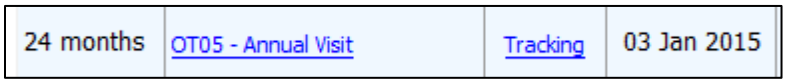
a. Visit Information
b. Medical History
c. Pregnancy Monitoring
d. Compliance
    i. How many doses has the participant missed since the last study visit?
        1. Record the number the participant recalls.

Step 5. After entering data, Save and Close eCRF form.

9.3.12 OT05- Annual Visit Form

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

Step 2. Under Event Title - Select OT05 - Annual Visit



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

Step 4. Complete all sections for this form.

Note: This is a three page form. Make sure both pages are completed by using the navigation arrows at the bottom of the page.

Step 5. After entering data, Save and Close eCRF form

9.4 Additional Study Forms/Events (PRN)

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

9.4.1 List and Definitions of PRN Forms

Forms available are as follows:

1. OT03 3 Month Visit Form – to be used if an unscheduled 3 month visit is completed outside of the normal visit schedule
2. OT04 6 Month Visit Form – to be used if any unscheduled semi-annual follow-up visits are completed outside of the normal visit schedule.
3. OT05 Annual Visit Form – to be used if any unscheduled annual follow-up visits are completed outside of the normal visit schedule.
4. OT06 3 Month Phone Contact – to be used if any unscheduled interim phone contacts are completed outside of the normal visit schedule.
5. OT07 Change in Study Drug – to be used whenever the participant's study drug use status changes (i.e. voluntary or involuntary withdraw from medication, etc)
6. OT09 Mortality Event – in the event that a participant fatality occurs during the course of the study, the Mortality Event Report is completed regardless of the cause of death. Information is collected on the date of death, characteristics of the event, and the cause(s) of death.
7. OT10 Pregnancy Confirmation – this form is completed in the event that a female study participant becomes pregnant at any point during the course of the study. The form is meant to capture information on the pregnancy including: expected delivery date, discontinuation of study drug, willingness to continue with follow-up visits, and pregnancy history. The form also inquires as to whether the participant has contacted her obstetric care provider regarding her participation in this study.
8. OT11 Pregnancy Outcome – This form is completed when the outcome of a pregnancy is known. It is meant to capture information on the outcome of the pregnancy, most importantly if the pregnancy resulted in a live birth, neonatal death, stillbirth, miscarriage, or an induced abortion, as well as the details of the outcome. If the pregnancy resulted in a live birth, information on the infant is collected. Some responses on this form, if chosen, indicate the completion of an Adverse Event report.
9. OT12 Change in Study Status – to be used when the status of a participant changes (subject withdrawals from study or is lost to follow up, etc). Once participants are enrolled in the Oral Insulin Study, they are enrolled for the duration of the Study (or until study endpoint is met). A change of status could involve the participant becoming inactive by not being able or willing to attend future follow-up visits. This form will also be completed if an inactive participant decides to return to active study participation by attending future follow-up visits. This form will collect information on the date of the change in status, as well as the reason for the change in status. Note that this form is completed each time a participant changes study status.
10. OT13 Protocol Deviation – to be used whenever a protocol deviation occurs (visits or samples are missed or completed outside of allowable visit window, etc). A protocol

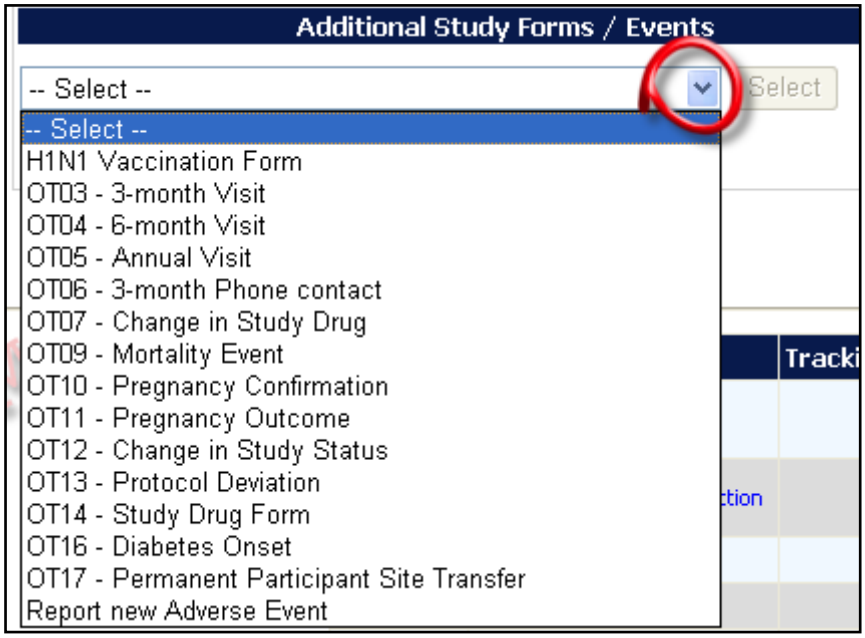
deviation is a variation from the processes or procedures defined in a protocol or MOO. A separate form must be completed for every unique protocol deviation that occurs, even if the subject is the same. The form obtains specific information on the deviation that has occurred, including the date the deviation occurred, the specific deviation that has occurred, as well as the reason for the protocol deviation.

11. OT14 Study Drug Form – to be used whenever study medication is dispensed or returned during an unscheduled visit.
12. OT16 Diabetes Onset – to be used whenever it is determined a participant has developed Diabetes. The collected information includes hospitalization information, signs and symptoms of diabetes, and glucose levels.
13. OT17 Permanent Participant Site Transfer – to be used if a subject moves from one study site to another. The form collects information on the date the transfer is occurring and the number of the site to which the participant is transferring.
14. Report New Adverse Event – to be used when a subject experiences a reportable adverse event

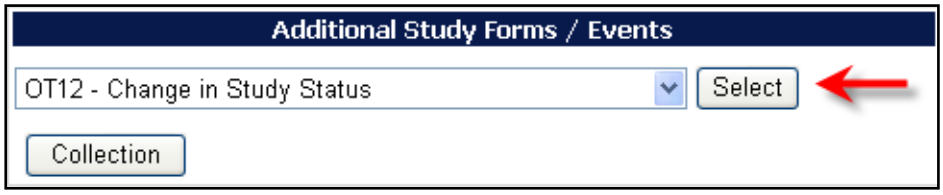
9.4.2 Open a New Additional Study Form/Event (PRN Form)

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

Step 2. Select the form needed from the list.



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

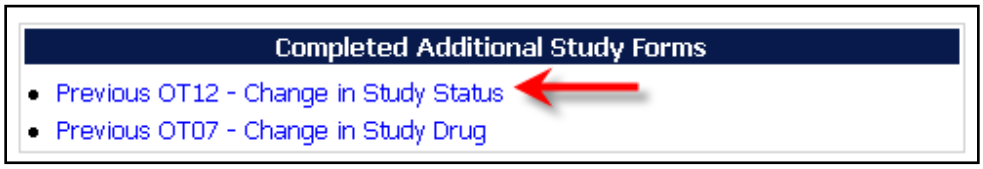


Step 4. A new window will open with the selected form.

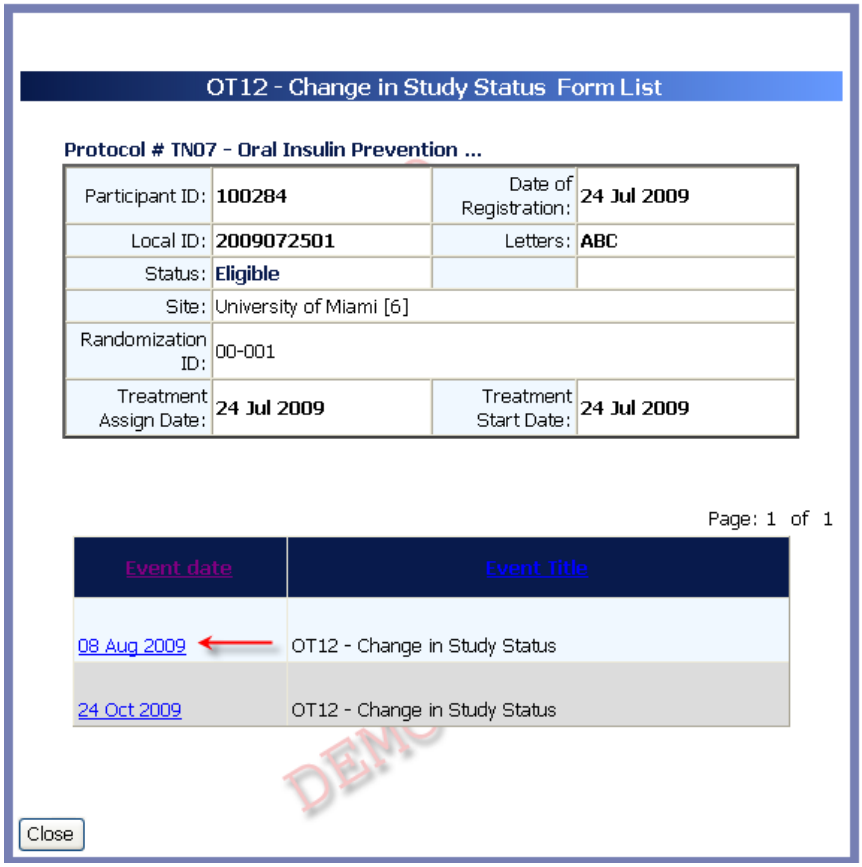
9.4.3 Open a Previously Completed Additional Study Form/Event (PRN Form)

Step 1. From the participant details page, on the right side of the main screen, directly beneath the subject header, above the study schedule, is a list of all types of PRN forms previously completed for the participant.

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



Step 3. A new window will open displaying a list of all PRN forms previously completed for the participant of the selected type. Select the specific form you wish to view.



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

9.4.4 PRN Specimen Collection Forms

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

10. ADVERSE EVENT REPORTING PROCEDURES

All reportable 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 is 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.

Throughout the study, only clinically qualified personnel must document occurrence and severity of 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 (regardless of relatedness) 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
- 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.

The FDA has given TrialNet a waiver for reporting hospitalizations at diagnosis of type 1 diabetes. However, this pertains to FDA reporting only. Local IRBs maintain their own reporting requirements for such events. Therefore, all sites should continue to report these events to the TNCC using the online system. Sites should consult with their local IRB to determine if

hospitalizations pertaining to the diagnosis of diabetes should be reported locally as serious adverse events. Please refer to Appendix M for additional guidance.

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:

TrialNet provides several resources for the proper use of CTCAE codes for adverse event reporting. Because the NCI has developed and maintained the CTCAE classification, the

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

Additionally, the CTCAE can be accessed online from the NCI at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

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

- A 'Remark' is a clarification of an AE.

- An 'Also Consider' indicates additional AEs that are to be graded if they are clinically significant.

- A 'Navigation Note' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same Category unless the 'Navigation Note' states differently.

Sometimes the AEs listed for a category are "clustered" together using a supra-ordinate term. A supra-ordinate term is located within a Category and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word "select". A supra-ordinate term helps organize a group of AEs within a category; an AE (from a select list of AEs listed below the specify comment) must be selected beyond the supra-ordinate term.

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

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

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

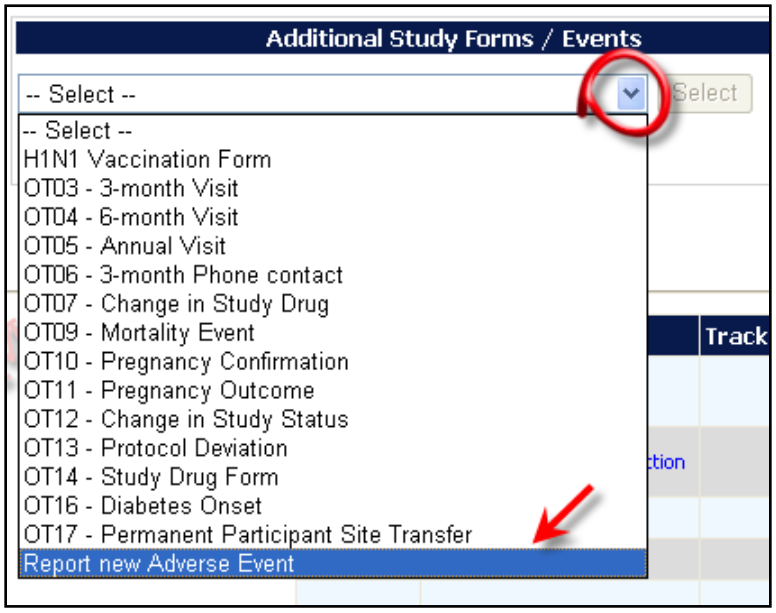
Follow the timelines below for the reporting of adverse events:

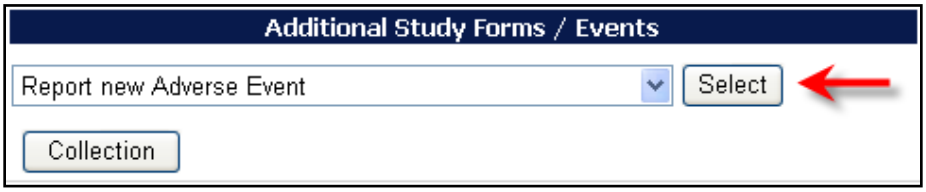
- Within **24 hours** (of learning of the event), investigators must report any Serious Adverse Event (SAE) that:
  Is considered life-threatening/disabling or results in death of subject
  -OR-
  Is Unexpected/Unanticipated
- Investigators must report all other SAEs within **5 working days** (of learning of the event).
- All other (suspected) grade 2 or greater 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.

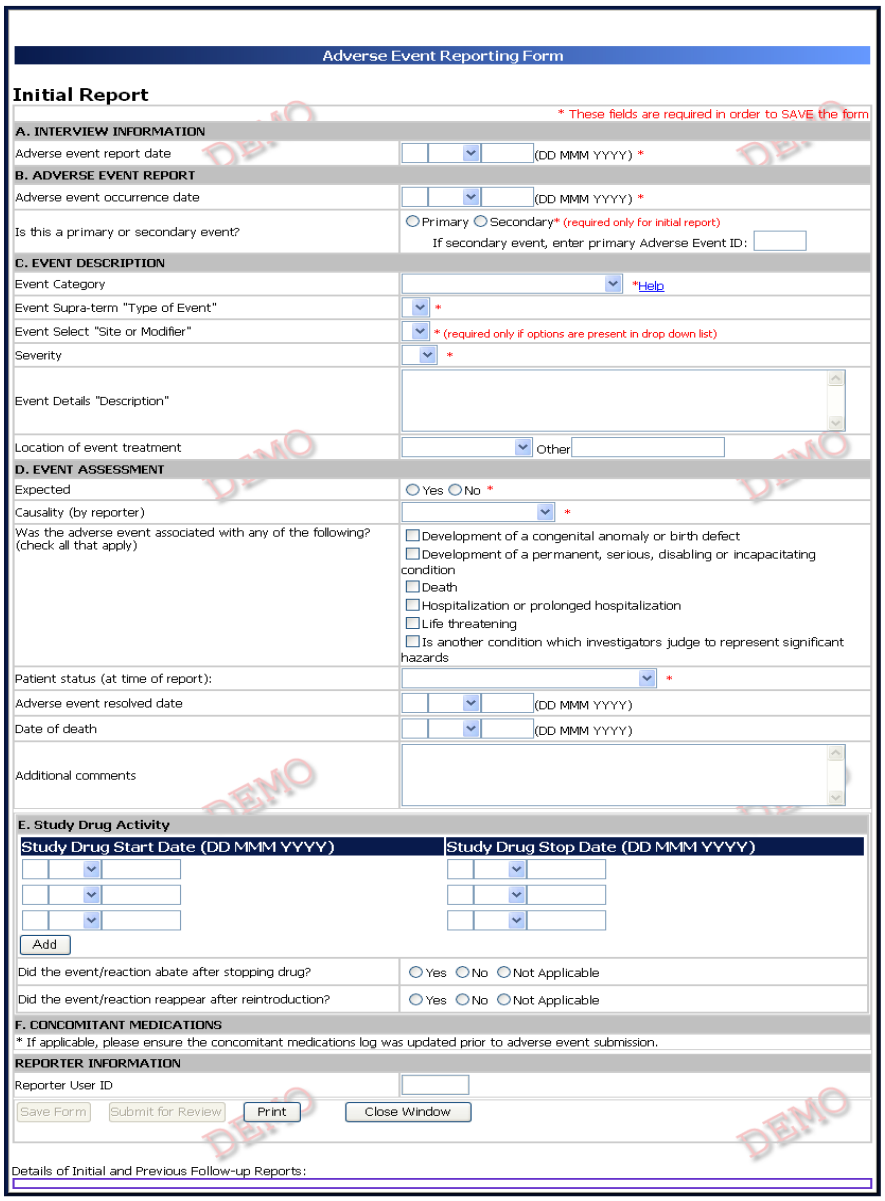
a. To save this report, WITHOUT SUBMITTING, select “Save draft.”

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.

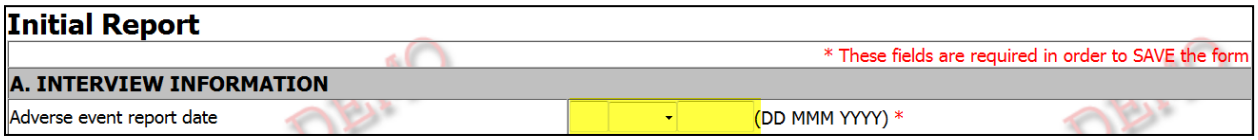
c. If the save is successful, you will see a success message. You may then close this window. If you do not see a success message, your report was not transmitted. Please resave, or contact your TNCC CRA immediately for assistance.



Adverse Event Reporting – Description of each field:

Section A. Interview Information:

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

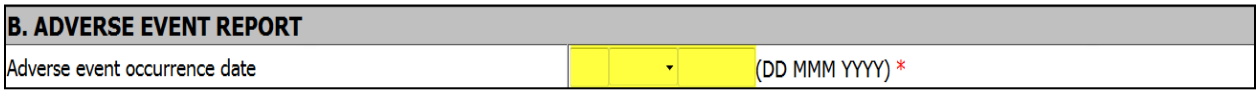


Initial Report	
	* These fields are required in order to SAVE the form
A. INTERVIEW INFORMATION	
Adverse event report date	(DD MMM YYYY) *

Section B. Adverse Event Report

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

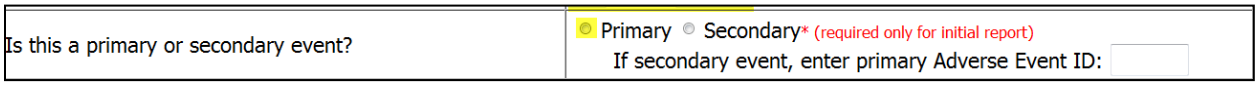
*Note: Date **cannot** be prior to patient registration date. For treatment studies: If an adverse event occurred before participant receives first treatment, the event should not be captured on AE form. Event should be captured in Interim History Form and documented.*



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

- Is this a primary or secondary event?:
  - 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.*

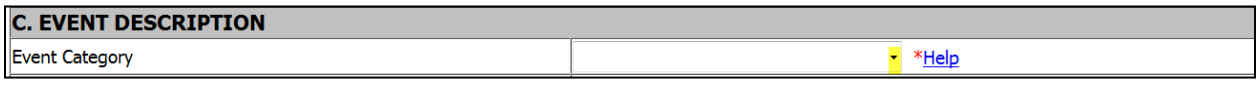
For example: Participant suffers a seizure (primary event) which caused resulted with a broken arm (secondary event).



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

Section C: Event Description

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



C. EVENT DESCRIPTION	
Event Category	*Help

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

Event Supra-term "Type of Event"	*

- *Event Select "Site or Modifier"*: 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. For TrialNet studies, diabetes and symptoms related to diabetes are expected.

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)

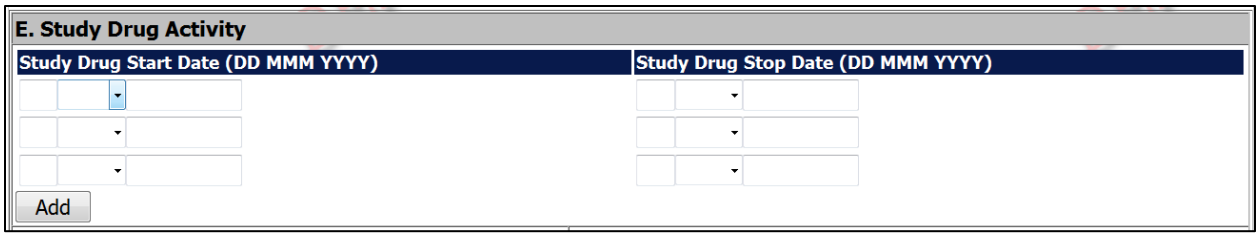
- *Additional Comments*: Add any additional pertinent information that is not captured elsewhere on the form.

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

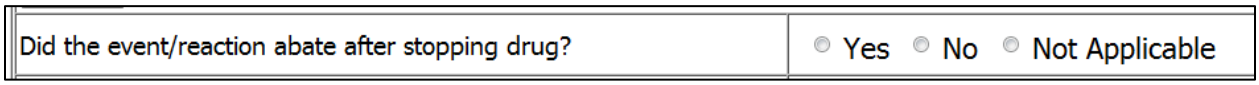
Section E. Study Drug Activity:

- *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.

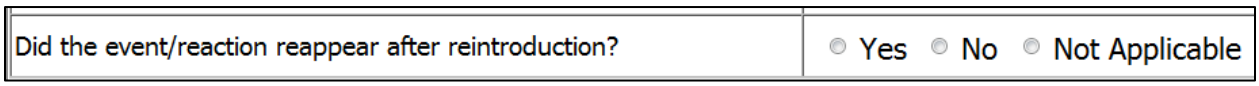
Note: Further clarification in section 10.3.3: Section E. Study Drug Activity: Study Drug Stop/Start Date.



- 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.

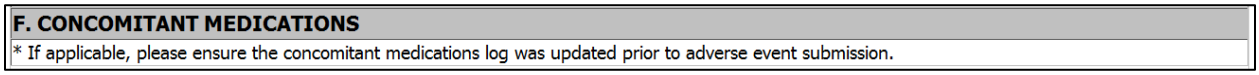


- Did the event/reaction reappear after reintroduction?:
  a. Enter "Yes" if AE being reported reoccurred after treatment was restarted; or
  d. Enter "No" if AE being reported did NOT reoccur after treatment was restarted; or
  e. Enter "Not Applicable" if the study drug was not stopped or if study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

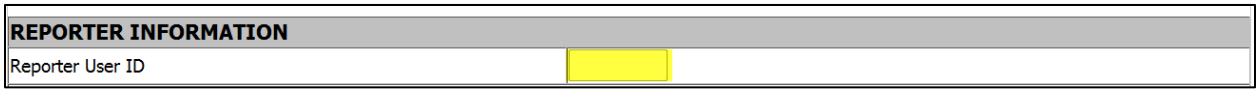


Section F. Concomitant Medication:

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



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



Form Disposition:
Options after completing the AE are: Save a draft, submit for review, print, or simply, close a window. Close window option DOES NOT automatically save the AE form.

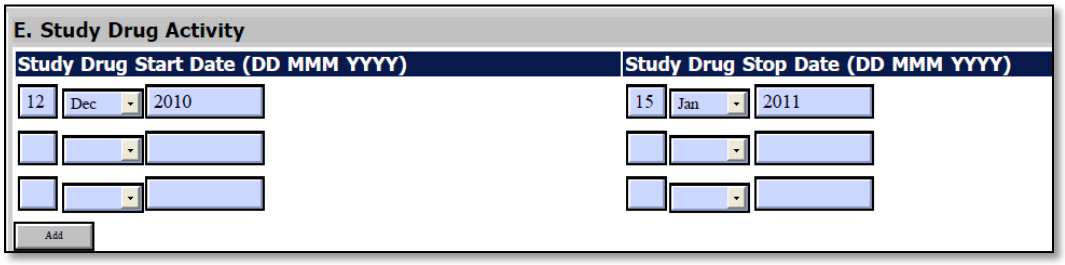
Please Note: Contact TNCC CRA if there are any additional questions regarding this form

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

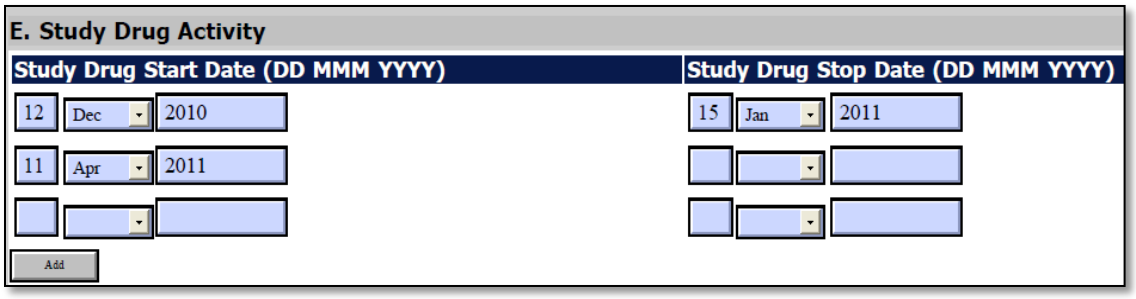
Start Date is based on the day the subject received their first study treatment. For instance: Participant 123456 received first study drug on 12/12/2010, the **Start Date** would be that date.

Please Note: Start Date should always be completed for any participant who has received study drug.

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.*

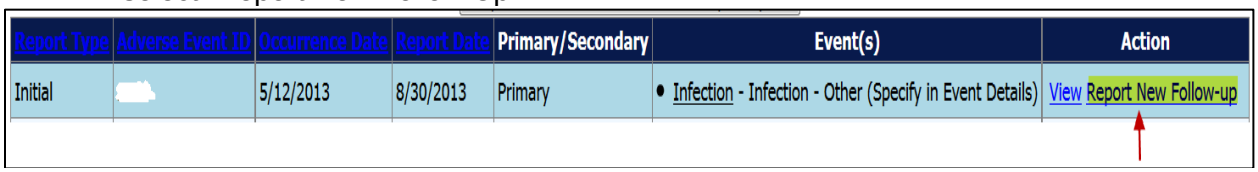
10.4 Directions for Reporting Follow-Up AE's/System Description

10.4.1 Navigating to the Follow-Up Reporting Form

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

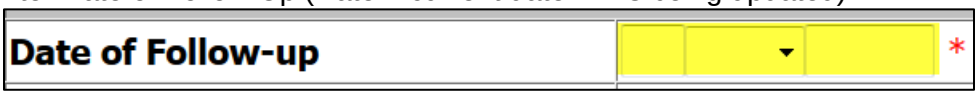
10.4.2 Reporting a Follow-Up to an Adverse Event

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

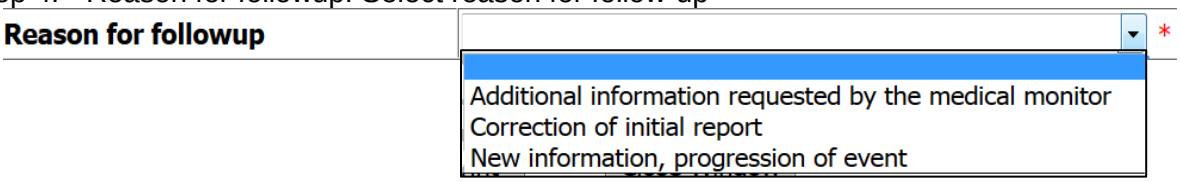


Step 2. Scroll down to section titled: Follow-Up Information

Step 3. Enter Date of Follow-Up (Date = current date AE is being updated)



Step 4. Reason for followup: Select reason for follow-up

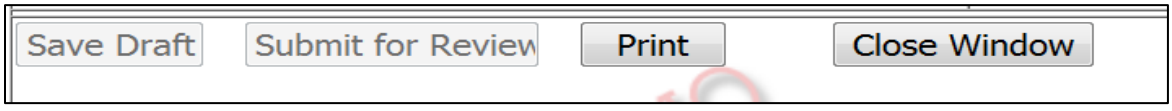


Step 5. Scroll up to either "Additional Comments" or "Event Details Description" and describe reason for follow up. When entering reason, it is recommended to provide current date of follow up

Example of Follow Up Reason(s):

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

Step 6. Form Disposition: The AE can either be: Save a draft; or submit for review, print, or simply close a window.



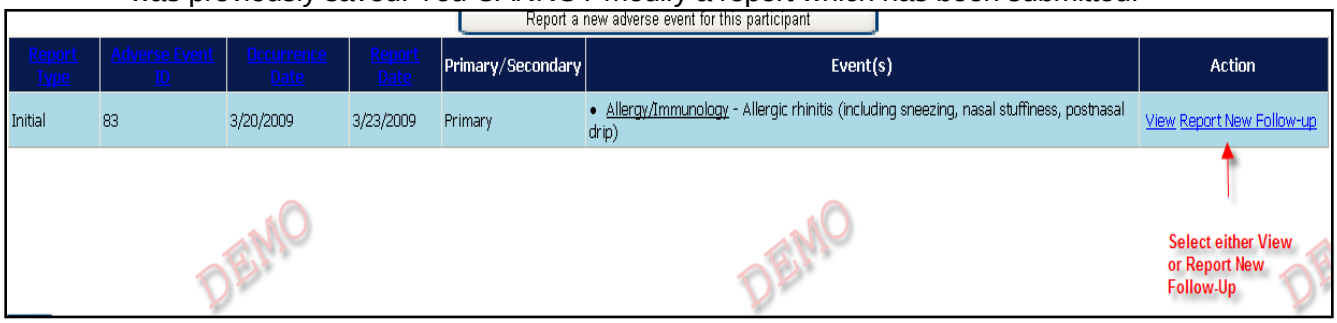
Note: Contact TNCC CRA if there are any additional questions regarding this form

10.5 Viewing and Editing Previously Reported Adverse Events

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

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

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



Step 4. Any modifications or updates that need to be made to a previous adverse event should be submitted by completing a follow-up report. To complete a follow-up report you would select "Report New Follow-up".

10.6 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 delegated member 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.

10.7 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 to be (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)). Only events that satisfy all three of these criteria, should 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:

1. Site completes 3500A MedWatch report (mandatory reporting form).
    a. Link to form and Instructions for completing the form can be found on the FDA Website.
    b. It is up to the site to determine if a MedWatch SAE should be completed
    c.
    d. Site emails completed 3500A MedWatch report to TNCC CRA and TrialNet Medical Monitor (Brett J. Loechelt, MD; bloechel@cnmc.org)
2. 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 rapidly 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.

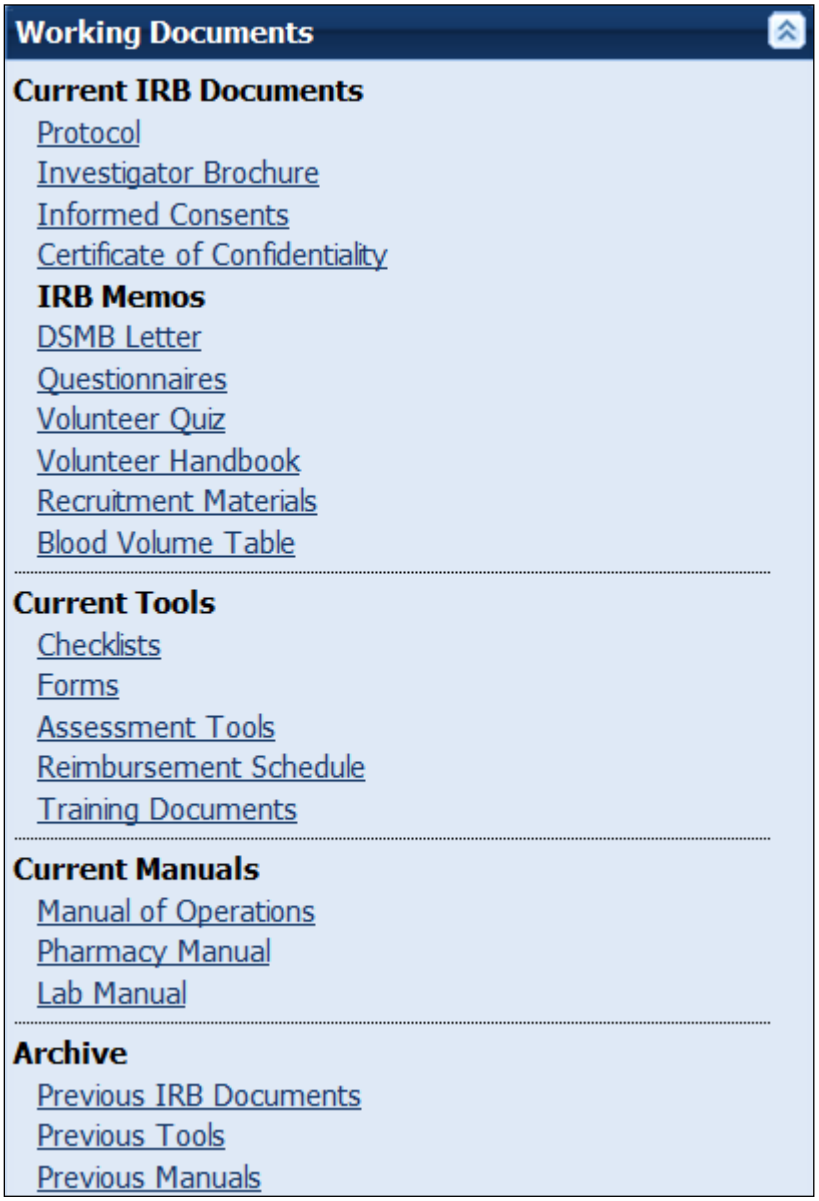
Source: FDA Draft Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies (September 2010).

11. Protocol Manager: Portlets and Tools

From the TN07 Oral Insulin Protocol homepage, there are a series of portlets meant to assist/aid sites in the conduct of the study.

11.1 TN07 – Working Documents Portlet

From the TN07 Oral Insulin Protocol 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

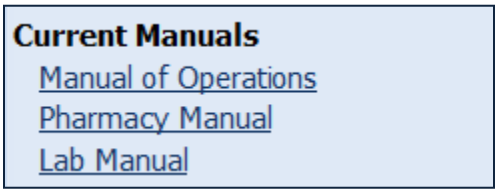
Under the “Current Tools” header are the most current versions of all study-related materials to aid sites in the conduct of the study including:

1. Checklists
    a. TN07 Visit Checklists
2. Forms
    a. Pharmacy Forms
        i. Agent Request Form
        ii. Agent Return Form
        iii. Investigational Drug Accountability Log
        iv. EMINENT Clinical Site Contact Form
        v. Oral Insulin Customs Invoice for Returns to Biotec (International Sites Only)
    b. Current Site Forms
    c. Eligibility Deviation Form
    d. Lab-related Forms
3. Assessment Tools
    a. Template source documents
        i. Sites may edit these templates or create your own.
    b. Pill Compliance Tools
        i. Optional template pill compliance calendars and template instructions that sites may edit and provide to subjects. If sites wish to provide these documents to subjects, they should be reviewed by a site’s local IRB/ERB.
    c. eCRF Copies
4. Reimbursement Schedule
5. Training Documents
    a. Oral Insulin Training Matrix
    b. Training Presentations and materials related to the study
    c. Certification Quizzes
    d. Strategies to Improve Retention and Compliance
    e. Concomitant Medication Log Instructions

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. TN07 Manual of Operations (MOO)
    a. Tracked and clean versions of the current MOO
2. Pharmacy Manual of Operations
    a. Tracked and clean versions of the current Pharmacy MOO
3. Laboratory Manual
    a. Current TN07 Protocol Lab MOO
    b. Specimen Management System (SMS) User Manual
    c. Specimen QC Program User Manual

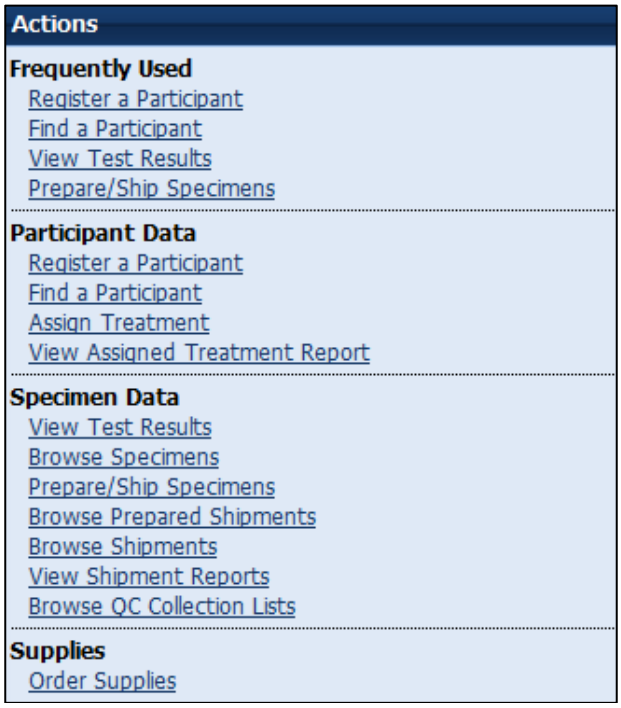


11.1.4 Archive

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

11.2 TN07 – Actions Portlet

From the TN07 Oral Insulin Study homepage, all study-related actions are available in the "Actions" portlet.



11.2.1 TN07- 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

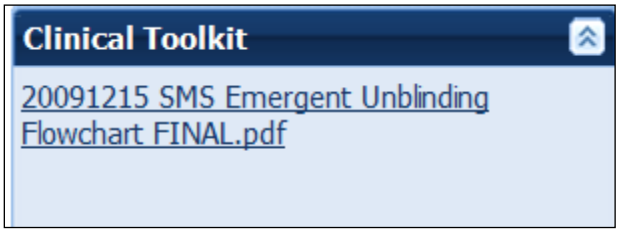
Under the "Supplies" actions header is a link to the Supply Ordering System (SOS).

11.3 TN07 – Contacts

From the TN07 Oral Insulin Study homepage, all study-related contacts are available in the "Contacts" portlet.

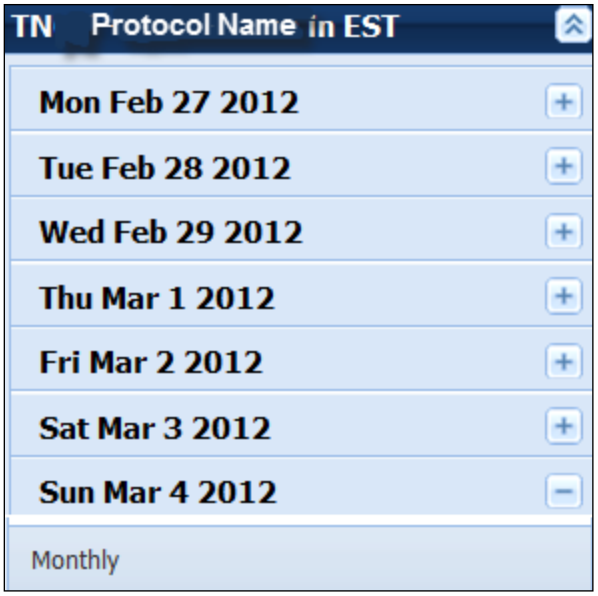
11.4 TN07 – Clinical Toolkit

From the TN07 Oral Insulin Study homepage, all study-related clinical tools are available in the "Clinical Toolkit" portlet.



11.5 TN07 – Calendar

From the TN07 Oral Insulin Study homepage, all study-related calls, trainings and event are noted in the "Calendar" portlet.



11.6 TN07 – Protocol Development Committees

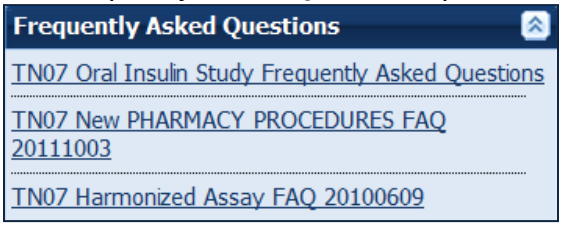
From the TN07 Oral Insulin Study homepage, links to the Protocol Chair Committee and Study Group Committee pages are located under the "Protocol Development Committee" portlet.

11.7 TN07 – Publications

From the TN07 Oral Insulin Study homepage, all protocol specific publications, ancillary publications and data sharing policies are located under the “Publications” portlet.

11.8 TN07 – Frequently Asked Questions

From the TN07 Oral Insulin Study homepage, all protocol specific frequently asked questions (FAQs) are located under the “Frequently Asked Questions” portlet.



12. Member's Website Reports

12.1 Network Wide Reports

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

Step 2. Select your site folder.

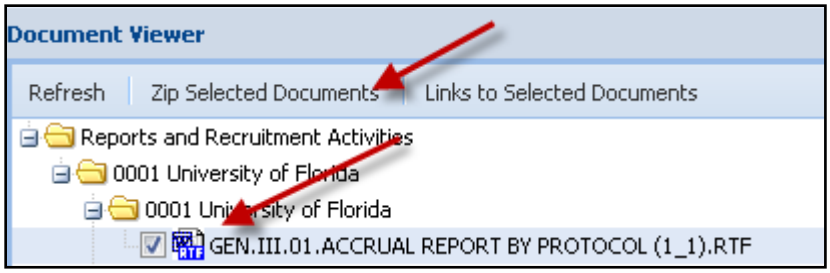
Step 3. Next, select the "General Reports" folder.

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

Network Wide Reports Currently Available:

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

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



12.2 Protocol Specific Reports

From the TN07 Oral Insulin Study 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 TN07 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	TN07.01.Accrual Report By Clinical Center, Year and Stratum.rtf	Accrual totals, by clinical center and stratum.	Monthly
	TN07.I.02.Actual.v.Expected Accrual - Graph.rtf	Graph of actual verses expected accrual.	Monthly
	TN07.II.03.IRB Summary - Ethnicity, Race and Gender Report (CC#).rtf	IRB summary of ethnicity, race and gender for all subjects	Monthly
	TN07.I.04.Adverse Event Summary Report.rtf	Summary of all reported AEs and SAEs	Weekly
	TN07.I.01.Accrual Report By Clinical Center.rtf	Displays for a specific protocol, by clinical center- accrual totals for all sites.	Monthly
Site Reports	TN07.III.01.Accrual Report (CC#_Site#).rtf	Accrual summary for clinical center and all affiliates	Monthly
	TN07.III.02.IRB Summary - Ethnicity, Race and Gender Report (CC#_Site#).rtf	IRB summary of ethnicity, race and gender for each site	Monthly
	TN07.III.03.Adverse Event Summary Report (CC#_Site#).rtf	Displays summary of all AEs and SAEs	Monthly
	TN07.III.04.Study Center Scheduling Calendar (CC#_Site#).rtf	Displays for a specific protocol, for a specific site- a calendar of target dates for subjects' visits	Monthly
	TN07.III.09.Particpant Schedule of Visits Report (CC#_Site #).rtf	Displays a calendar of target dates for subjects' visits	Daily
Recruitment Reports for Potentially Eligible TN07 Participants (Located on the TN01 Protocol Management Page → Reports and Recruitment Portlet→ Clinical Center)	TN01.II.11.List of Potential TN07 Participants (CC#)	Displays list of potential TN07 participants currently active at the clinical center and affiliate sites.	Daily
	TN01.II.11.List of Potential TN07 Participants (CC#_Site#)	Displays list of potential TN07 participants currently active at that specific site.	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, barcode scanners recruitment and retention materials

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

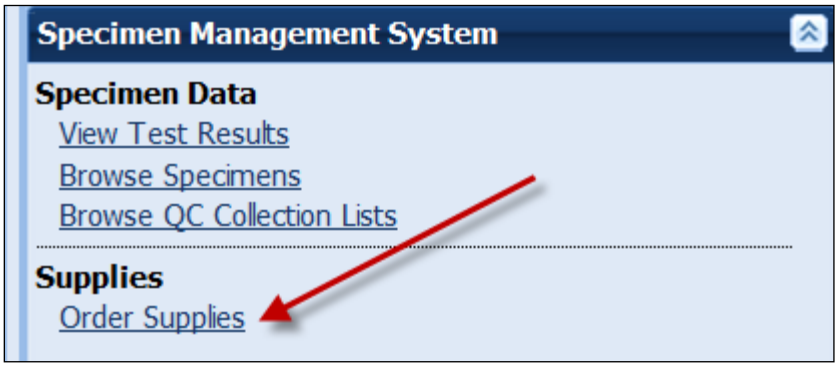
13.2.1 Ordering Study Agent

Please refer to the Pharmacy Manual of Operations.

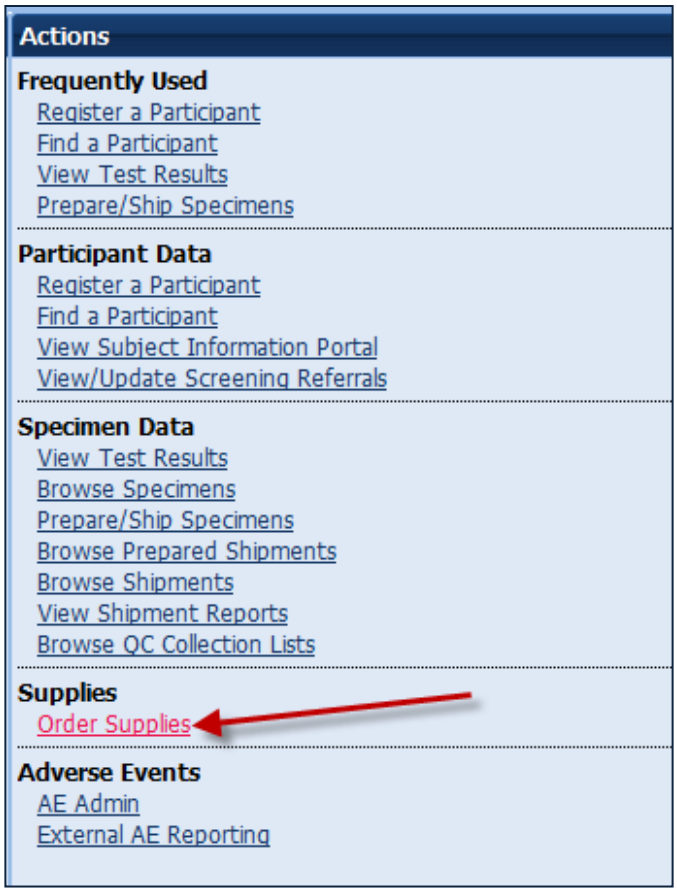
13.2.2 Navigating the Fisher BioServices Supply Ordering System (SOS)

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 TN07 Oral Insulin Study homepage, navigate to the central “Actions” portlet and select “Order Supplies.”

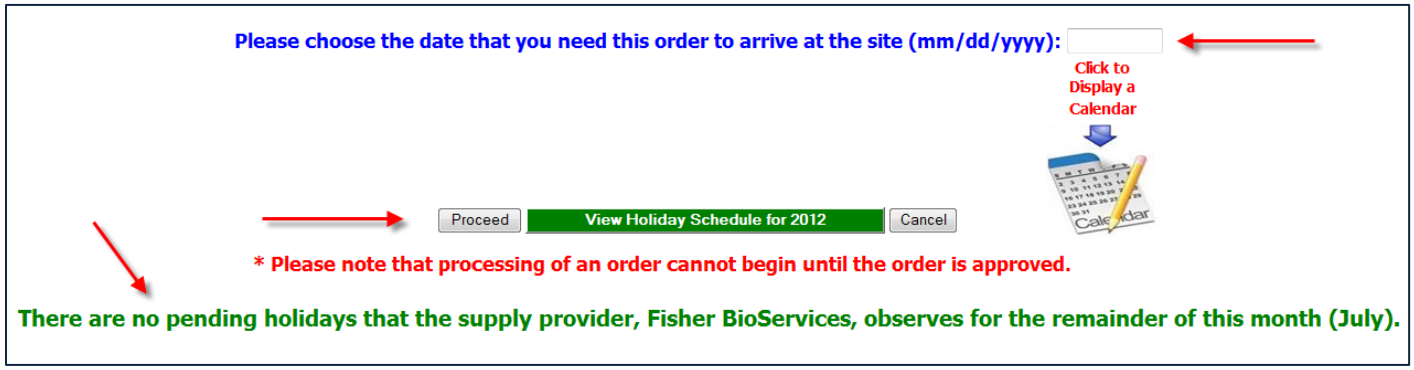


Step 2. The Supply Ordering System (SOS) web page will appear in a new window. You will be prompted to enter your TrialNet Supply Order System Login information.

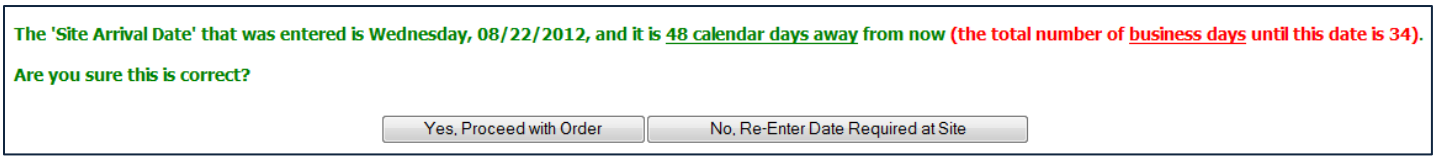
Note: If you do not have a login, please contact the TNCC to obtain a user account.

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.**

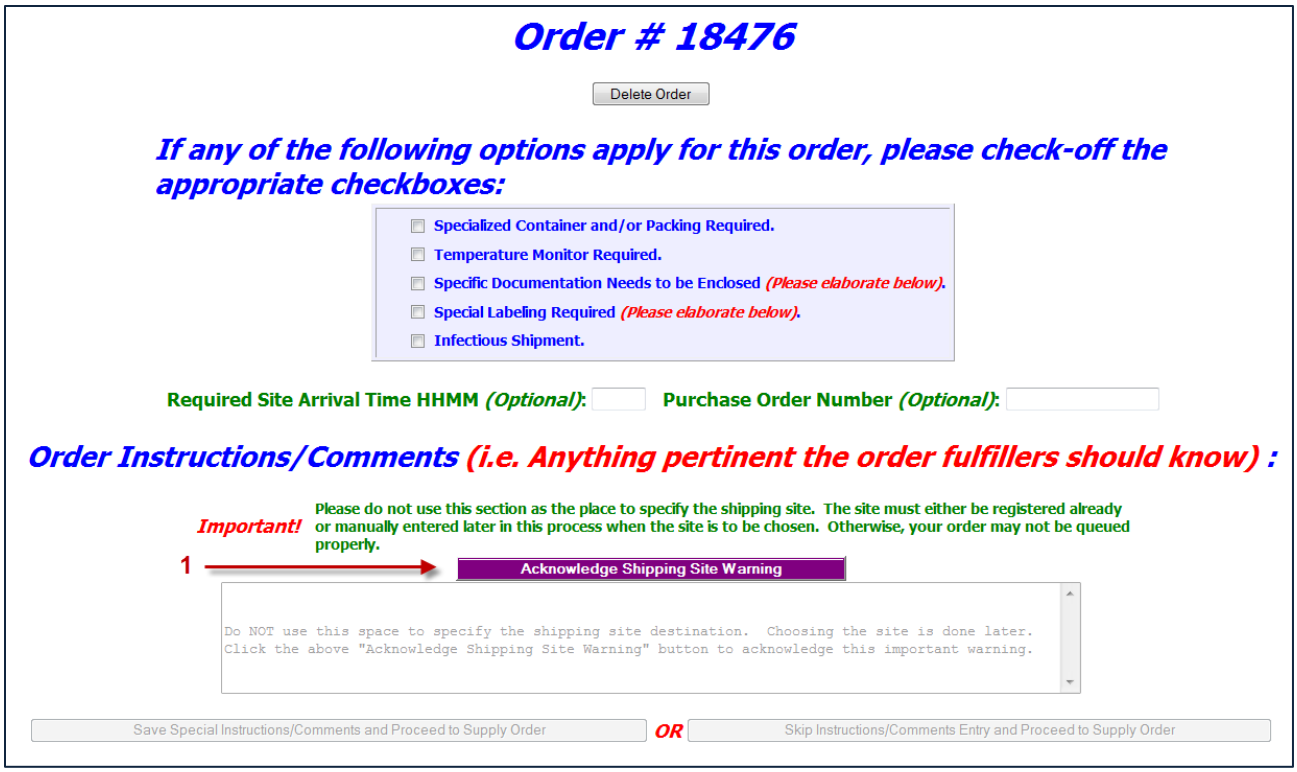


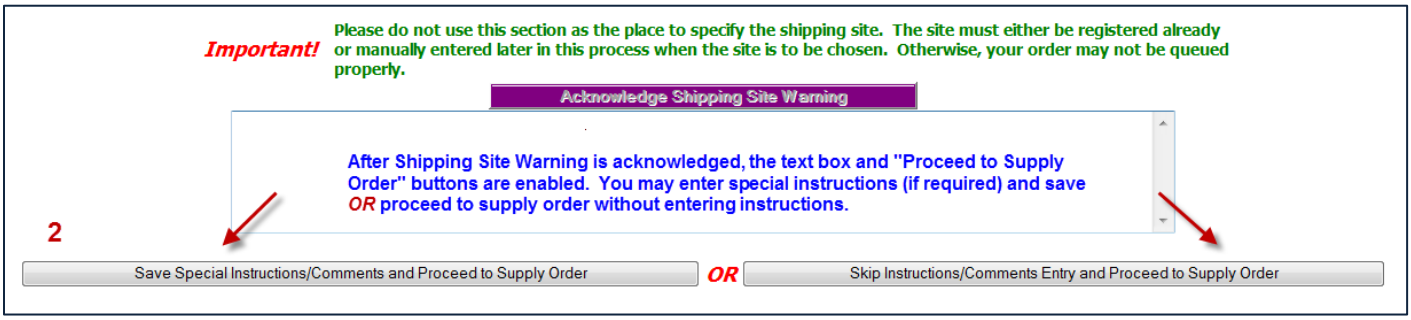
Step 5. After entering the date and selecting "Proceed" you will be prompted to confirm the date and either select proceed or opt to re-enter the date. If the date you have selected is OK, please select "Yes, Proceed with Order." If not then select "No, Re-Enter Date Required at Site."



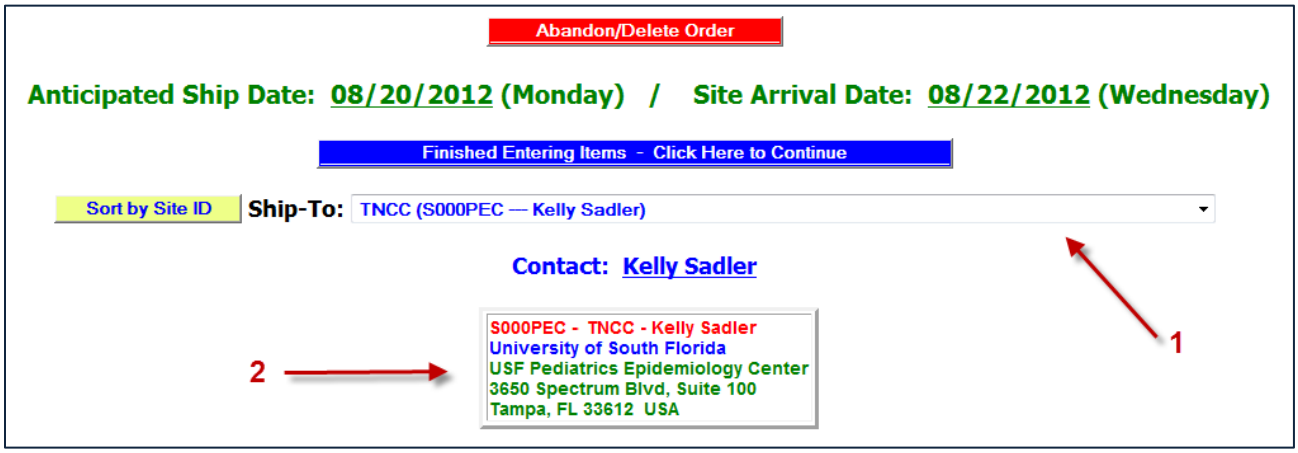
Step 6. Once you have confirmed the date is correct and selected "Yes, Proceed with Order" you will be prompted to enter order instructions or comments OR proceed to the order without special instructions:

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."

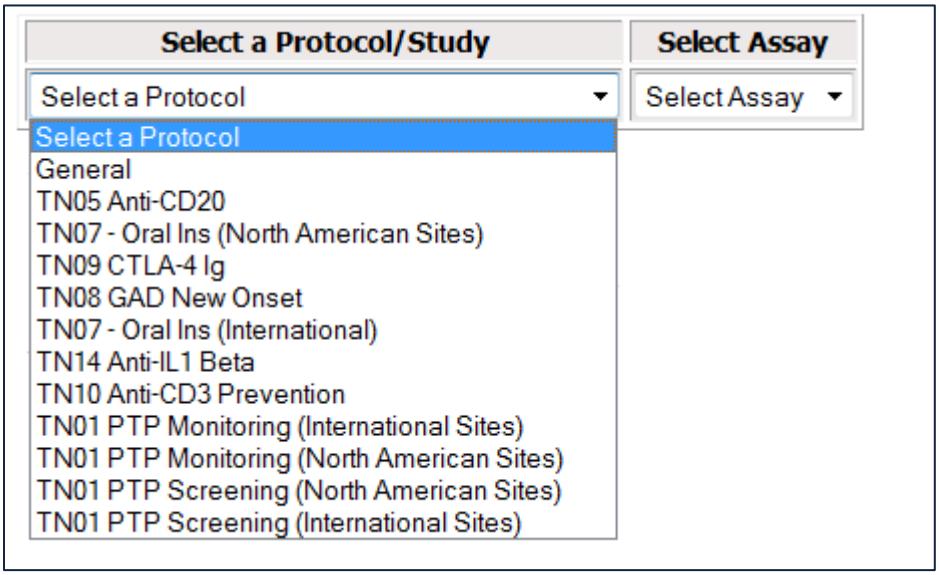




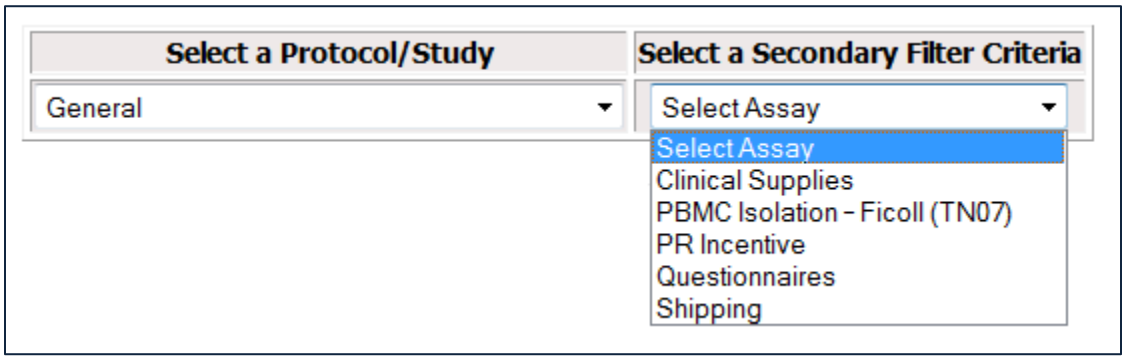
Step 7. Enter the “Ship to Site” by selecting a site from the “Ship-To” dropdown menu.



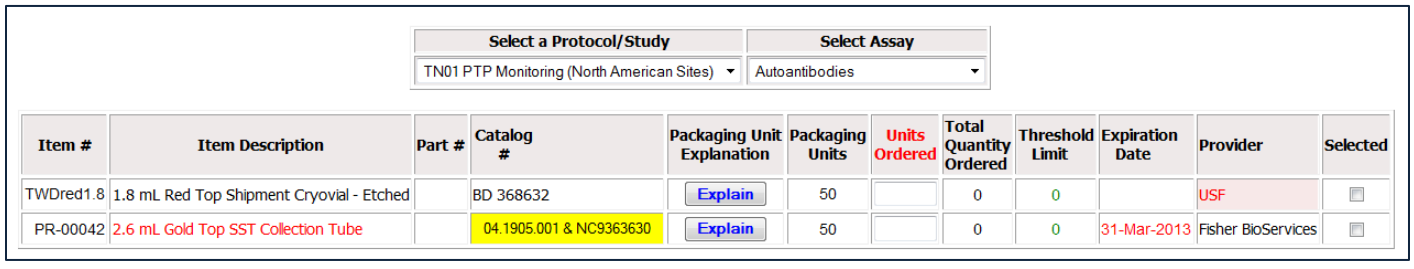
Step 8. Select the Protocol/Study and Assay for which you want to order supplies.



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.

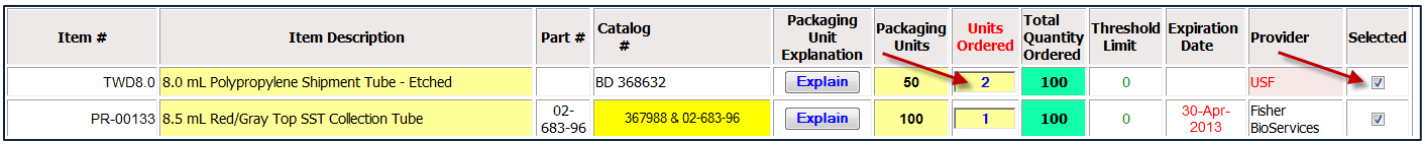


Item #	Item Description	Part #	Catalog #	Packaging Unit Explanation	Packaging Units	Units Ordered	Total Quantity Ordered	Threshold Limit	Expiration Date	Provider	Selected
TWDred1.8	1.8 mL Red Top Shipment Cryovial - Etched		BD 368632	Explain	50		0	0		USF	
PR-00042	2.6 mL Gold Top SST Collection Tube		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.

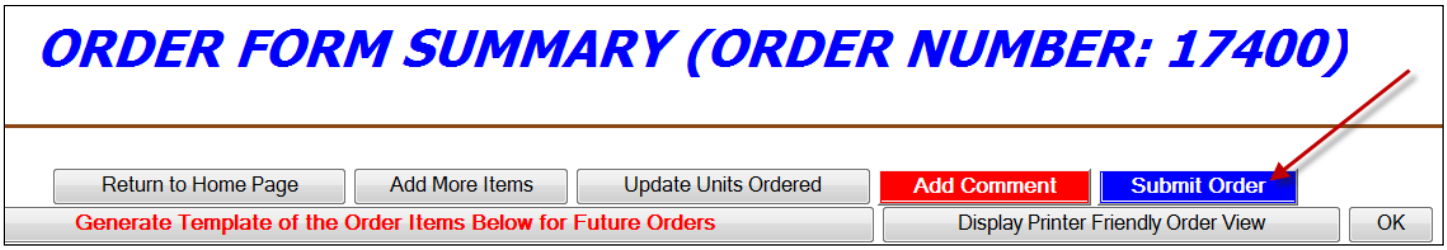
For example, 1 unit of the 8.0 mL shipment tubes contains 50 tubes. Since 2 units were ordered below, a total of 100 tubes will be shipped.



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.

13.2.3 Supply Organization

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

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

The TN07 Oral Insulin Study is divided into two "protocols" based upon site location (North America vs. International). Each of the 2 protocol listings contain only the tests applicable to that site

location. Specimen collection and shipment tubes and/or vials are listed under each assay heading.

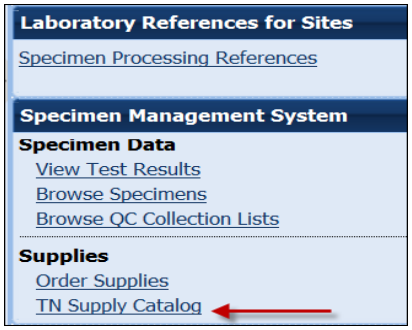
All other supplies are listed under “General” in the “Protocol” filter. For general supplies, the “Test/Assay” secondary filter refers to the major item category: clinical, shipping, PR incentive, and questionnaires.

The table below lists all filter criteria applicable to the TN07 Oral Insulin Study. Please refer to Appendix M for a complete list of items available for the TN07 Oral Insulin Study.

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

TN07 Oral Insulin Supply Organization	
“Protocol” Filter Criteria	**“Test/Assay” Secondary Filter Criteria**
TN07 – Oral Ins (North American Sites)	Autoantibodies Handbooks HbA1c IVGTT OGTT Questionnaires Whole Blood - RNA
TN07 – Oral Ins (International Sites)	Autoantibodies Handbooks HbA1c IVGTT OGTT Questionnaires Whole Blood - RNA
General Supplies	Clinical Supplies PBMC Isolation – FICOLL (TN07) Shipping Supplies PR Incentive Questionnaires

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



14. 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 both domestic and international sites, studies will be eligible for an audit site visit within 12 months of the first subject accrual and annually thereafter.
2. 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.
3. 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). 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.
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.
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.

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:	• Current protocol • 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

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 Findings

1. A major deficiency is a protocol variance that makes the resulting data questionable.

2. A minor deficiency 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 deficiencies 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 Determinations

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 4 weeks of the receipt of the audit assessment letter. The response 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 TNCC Principal Investigator, Clinical Monitoring Subcommittee 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 4 weeks of the receipt of the second preliminary report of audit findings. The response must address each specific problem found during the audit and any general problems that were noted. The response 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 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 Site PI, the NIH, the Clinical Monitoring Subcommittee Chair, the TNCC Principal Investigator, and the Site Study Coordinator within 48 hours of the completion of the audit.

    b. <u>Second Preliminary 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 TNCC Principal Investigator, and the Site Study Coordinator.

c. Final Report of Audit Findings:
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 site study coordinator, the NIH, the Clinical Monitoring Subcommittee, the TNCC Principal Investigator, and the Clinical Center (as applicable for Affiliate sites).

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

15. Appendices