



**Type 1
Diabetes
TrialNet**

**Protocol TN20
Immune Effects of Oral Insulin**

Peter Gottlieb, MD

**Manual of Operations
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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.) Study Chair/designee drafts the initial version of the MOO. (The TNCC will provide templates and samples from other studies.)
- 2.) TNCC edits; collaborative development continues between study team and TNCC.
- 3.) When both study team and TNCC are satisfied, they can sign-off (i.e., approve) the current version of the MOO. The sign-off must be in writing or via e-mail.

1.2. Current Protocol Synopsis (Version 15Jan16)

Title	Immune Effects of Oral Insulin
IND Sponsor	National Institute of Health
Conducted By	Type 1 Diabetes TrialNet
Protocol Chair	Peter Gottlieb, MD Professor of Pediatrics and Medicine Barbara Davis Center Mail Stop A140 PO Box 6511 Aurora Court, Room 1325 Aurora, CO 80045 Phone: 303-724-6714; Email: Peter.Gottlieb@ucdenver.edu
Accrual Objective	Minimum of 40
Study Design	Randomized, unblinded, two arm mechanistic study
Treatment Description	67.5 mg Oral Insulin daily or Oral Insulin every other week, titrating up to 500 mg
Study Duration	1 Year
Objective	To determine if treatment with oral insulin has the potential to affect underlying immunological mechanism(s) that are observed through changes in immune markers.

	To determine if there are differential changes in immunological biomarkers between different schedules of oral insulin.
Primary Outcome	The change in immunologic biomarkers before and after treatment.
Secondary Goals	Safety measures and disease progression assessed by regular glucose tolerance testing.
Major Inclusion Criteria	mIAA and one other diabetes related autoantibody positive

1.3. Study Contacts

TN20 Study TrialNet Coordinating Center (TNCC)		
USF TrialNet Coordinating Center (TNCC) University of South Florida Health Informatics Institute Tampa, FL 33612	Primary Contact: Courtney Henderson	Ph.: (813) 396-9541 Fax: 813-910-1246 Email: Courtney.Henderson@epi.usf.edu
	Secondary Contact: Ilma Asif	Ph.: (813) 396-9321 Email: Ilma.Asif@epi.usf.edu

TN20 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

TN20 Core Laboratory Contact Information
Please refer to the TN20 Immune Effects of Oral Insulin Study Laboratory Manual for a complete list of TrialNet Core laboratories applicable to the TN20 protocol.

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. Implement and maintain 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 participant 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. Ensure 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 (eCRFs) 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. Further, to identify opportunities to implement data standards and share resources across the network. The TNCC participates in the design of clinical protocols, management of the protocol and amendment approval process, in addition to providing the data management and analysis necessary to support them. They facilitate data entry by building and maintaining data entry forms. The TNCC has developed and maintains the “Protocol Manager” clinical data management system used for the collection, storage and analysis of data for all clinical sites that participate in network studies. They are also responsible for generation of reports and analyzing data for this study in conjunction with the PI and other members of the TrialNet Study Group.

The TNCC also facilitates the use of appropriate technologies for communication and training, including videoconferencing and web-based video streaming, and maintains both the public and members websites for the TrialNet Network.

The TNCC fax number to fax IRB approvals is 813-910-5994. You may forward electronic approvals via email to: Regulatory@epi.usf.edu.

3. STEPS TO SITE ACTIVATION AND ONGOING REGULATORY REQUIREMENTS

3.1. Requirements for Activation

Enrollment cannot begin until the site has received an activation letter from the TNCC. All documents required for activation should be sent to the TNCC electronically to regulatory@epi.usf.edu (or by Fax to 877-775-7235).

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. **Human Subjects Training documentation for PI and main study coordinator**

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.

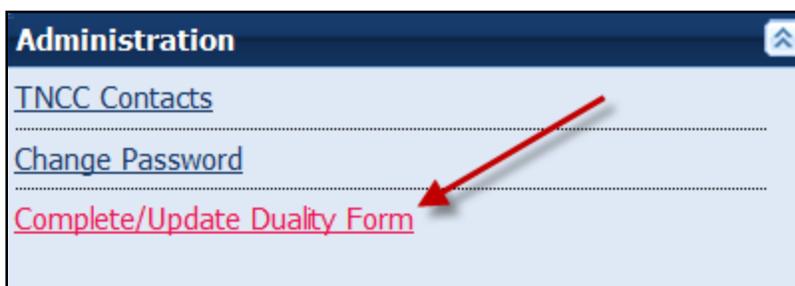
3.4. Duality of Interest Forms

Site activation will require a completed duality of interest form from a minimum of the PI, main site coordinator, and all persons listed in section 6 of the 1572.

Each person directly involved in the treatment or evaluation of participants 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.

Duality Of Interest Disclosure Forms - Previous
No Disclosure of Interest Forms have been completed for this user.
Duality Of Interest Disclosure Forms
Complete new Duality Of Interest Disclosure Form

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

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

<div style="display: flex; justify-content: space-around; margin-bottom: 10px;"> Save Print Close Window </div> <p style="color: red; margin: 0;">Your Duality of Interest form has been saved successfully. Thanks for completing this form!</p>

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

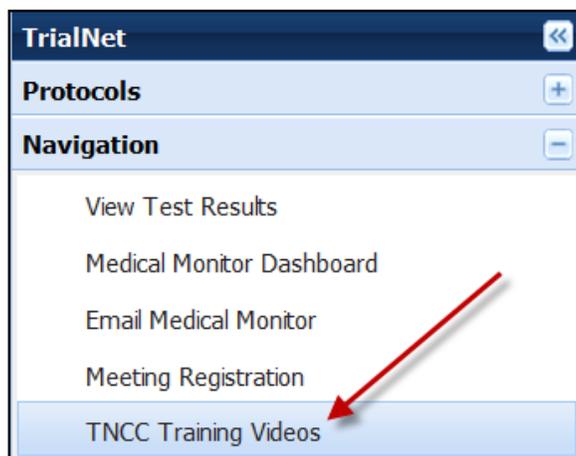
3.5. Study/System Training

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

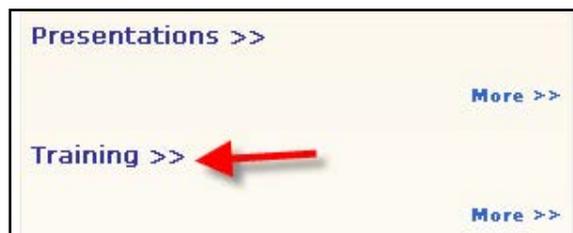
3.5.1 Online Training

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. TN20 Protocol Overview: Provides a description of the protocol, eligibility criteria, purpose, specific aims, and details of procedures.
2. TN20 Pharmacy Training: Provides an overview of pharmacy related procedures including drug ordering, dispensing, agent return, etc
3. TN20 Online Participant Registration: Provides a guided tutorial of how to register a participant

4. GENERAL Members Directory Overview: Provides a non-study specific overview of how to use the online member directory.
5. GENERAL Members Website Overview: Provides a non-study specific overview of how to use the online members' website.
6. GENERAL Protocol Manager Overview: Provides a non-study specific overview of how to use the online protocol manager page and related sections.

3.5.2 Study Certification Quiz

The TN20 Certification Quiz is available online and can be completed by all individuals listed in roles on the Site Delegation Log requiring knowledge of study procedures. Once the certification quiz has been completed the site can request the answers from their clinical center or TNCC CRA to review.

3.6. Statement of Investigator, Form FDA 1572

The FDA 1572 Statement of Investigator must be completed by all sites participating in studies with an Investigational New Drug (IND). Completed forms should be submitted electronically to the TNCC by email at regulatory@epi.usf.edu or by Fax to 877-775-7235. The original form 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 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, the updated form should be submitted electronically to the TNCC, as noted above. The original should be placed in the regulatory binder at the site.

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 participant needs to visit a specified internist who will perform a full physical to qualify participants 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 <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.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 participants 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 3.3). In addition to the updated SDL, the following documents should be submitted to the TNCC:

1. New User Form
2. TrialNet Confidentiality Agreement
3. Human Subject Training Certificate (if applicable)

The new staff user must complete a Duality of Interest form once they are granted access to the online system (See section 3.4).

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 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 GOALS AND STRATEGIES

4.1. Recruitment Goals

The study will plan to recruit a minimum of 40 participants.

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 eCRF.
- 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:

Eligible participants must **meet all** of the following inclusion criteria prior to randomization:

1. Participant in TrialNet Natural History/Pathway to Prevention Study (TN01) and thus, a relative of a proband with T1D and between the ages of 1-45 at the time of enrollment in TN01.
2. . If most recent OGTT demonstrates Normal Glucose Tolerance, participants must be age ≥ 3 years at time of randomization in this trial. If a previous OGTT is abnormal, two consecutive normal OGTTs are required for eligibility.
3. If most recent OGTT demonstrates Abnormal Glucose Tolerance, participants must be age 3-7 years at the time of randomization in this trial.
4. mIAA confirmed positive within the previous six months (210 days).
5. Participant must weigh ≥ 12 kg at the time of screening in this trial.
6. At least one other diabetes-associated autoantibody present on two separate samples, one of which was drawn within the past six months (210 days). Confirmation does not have to involve the same 2 autoantibodies.
7. Willing to provide Informed Consent or, if the participant is < 18 years of age, have a parent or legal guardian provide informed consent.

Exclusion Criteria:

Eligible participants must **not** meet any of the following exclusion criteria:

1. Diagnosed with diabetes or having their most recent OGTT with fasting glucose ≥ 126 mg/dl or 2 hour glucose ≥ 200 mg/dl.
2. . Prior participation in clinical research for secondary prevention of T1D.
3. History of treatment with insulin or oral hypoglycemic agent.
4. Current chronic user of medications altering stomach acid (such as H2 blockers, proton pump inhibitor and antacids).
5. History of gastric ulcer or gastric surgery.
6. History of therapy with immunosuppressive drugs or non-physiologic glucocorticoids within the past two years for a period of more than three months.
7. 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.
8. 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. Participants on such medications should be changed to a suitable alternative, if available, and will become eligible one month after medication is discontinued.
9. Pregnant, intends to become pregnant while on study, or lactating.
10. Deemed unlikely or unable to comply with the protocol or have any complicating medical issues or abnormal clinical laboratory results that interfere with study conduct or cause increased risk.

4.4. Exceptions to Questions Regarding Eligibility Criteria

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

4.1.1 Procedures for submission to the TrialNet Eligibility Committee

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

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

Policies, Procedures and Resources

Policies/Procedures
[ELS ELIGIBILITY REVIEW PROCEDURE 20100519](#)

Guidelines

Resources, Templates and Forms
[20121119 Eligibility Deviation Review Form Ver 2.1 FINAL](#)

- 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.

4.2 Follow Up of Eligible Study Participant

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:

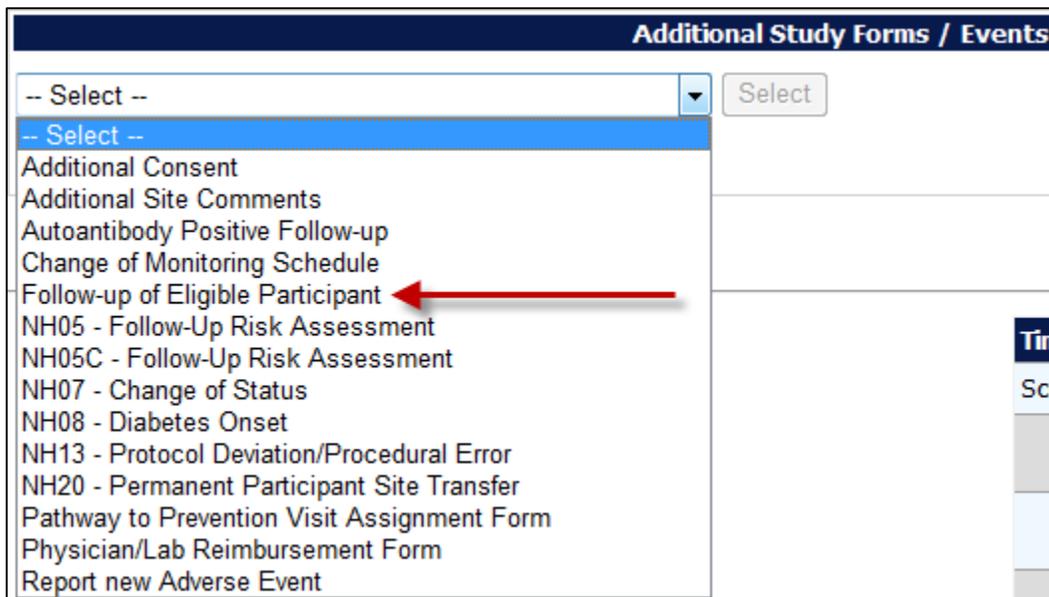
a. Reason not reviewed: _____

2. Comments: _____

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

This form can be completed regardless of whether they decline or agree to participation in the study.

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



Additional Study Forms / Events

-- Select --

Select

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

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

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

Yes
 No
 Not Sure

If the participant declines to screen for the study please select “no” for question 4 and indicate in the following section the reasons why they declined to participate. *(Please Note: more than 1 reason can be checked.)*

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

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

A new form can 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, or they are included on a site’s Hot Leads Report, then a new form should be completed.

5. STUDY VISITS

Templates for source documentation for all visits are located on the member’s website in the TN20 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 TN20 Laboratory Manual of Operations.

5.1 Initial (-1) Visit

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 2 of the Laboratory Manual of Operations 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	If an OGTT is to be performed, remind the participant that they need to be fasting for this visit	NA	NA
At Visit	Administer the consent and, if applicable, assent and local HIPAA form.	Consent & Assent	NA
At Visit	Administer the volunteer survey. Coordinator should review the survey with the participant and parents (if applicable) taking special care to review any incorrect answers.	Volunteer Understanding Assessment	NA
At Visit	Register the participant in the online system	NA	Participant Registration
At Visit	Collect participant's medical history	Complete Medical History	IE01 Initial Visit Form
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.	Concomitant Medication	Concomitant Medication
At Visit	Measure random glucose via clinic meter	Initial Visit Source Document	NA
At Visit	Measure and record participant's weight	Initial Visit Source Document	IE01 Initial Visit Form
At Visit	Conduct a physical exam (at Initial Visit or Baseline)	Complete PE	IE01 Initial Visit Form
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	IE01 Initial Visit Form
At Visit	Conduct a 2-hour OGTT, if required	Local OGTT Source	Specimen Collection
At Visit	Specimen collection: <ol style="list-style-type: none"> 1. CBC with differential 2. OGTT (if required) 3. Serum – Autoantibodies (if required) 4. HbA1c (initial visit or baseline visit) 5. Mechanistic Assessments <ol style="list-style-type: none"> a. Whole Blood – PBMC/Plasma b. Whole Blood – RNA 	Signed and dated printout of specimen collection form	Screening Specimen Collection CBC with Differential Form

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

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

5.2 Baseline (0A) Visit (All participants)

Window: Within 30 days of Initial (-1) Visit; cannot occur on the same day as Initial 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.	Baseline 0A Visit Source Document	IE03 Baseline Eligibility Form
At least 1 week prior to Baseline 0A Visit	Randomize participant online. Within the Immune Effects of Oral Insulin protocol homepage, select “Assign Treatment”. Please Note: Make note of the randomization number in the source documents. Contact TNCC to notify them of the expected randomization, so drug can be delivered to site	NA	Assign Treatment
At least 1 week prior to Baseline 0A Visit	Order 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 on the Agent Request Form.	Agent Request Form	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	Baseline 0A	IE02 Study

		Visit Source Document	Visit Form
At Visit	Ask the participant about any changes in medications since last visit	Concomitant Medications	Concomitant Medications
At Visit	Conduct a physical exam (if not done at initial visit)	Baseline 0A Visit Source Document	IE02 Study Visit Form
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher)	Baseline 0A Visit Source Document	Adverse Events
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Baseline 0A Visit Source Document	IE02 Study Visit Form
At Visit	Measure pre-dose glucose via clinic meter. Do not administer study drug dose if result is < 50 mg/dl	Baseline 0A Visit Source Document	IE04 Study Drug Form
At Visit	Specimen Collection: 1. Pre Dose Specimens	Signed and dated printout of specimen collection form	Baseline 0A Specimen Collection
At Visit	Administer study drug dose to participant	Baseline 0A Visit Source Document	IE04 Study Drug Form
At Visit	Observe participant for two hours post study drug dose	Baseline 0A Visit Source Document	IE04 Study Drug Form
At Visit	Specimen collection: 1. Post Dose Specimens 2. CBC with differential 3. HbA1c (if not done at initial visit) 4. Mechanistic Assessments a. Whole Blood – PBMC/Plasma b. Whole Blood – RNA c. Serum – Mechanistic Serum	Signed and dated printout of specimen collection form	Baseline 0A Specimen Collection CBC with Differential Form
At Visit	Dispense study drug (67.5 mg participants only)	Baseline 0A Visit Source Document	IE04 Study Drug Form Treatment Start Date
Post Visit	Enter data collected on source documents into the eCRFs online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the SMS Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post	Retain all informed consent documents, materials	NA	NA

Visit	from visit, and source documents in an organized fashion in a secured, double-locked room.		
Post Visit	Perform the treatment phase phone contact every 14 days between visits (67.5 mg participants only)	Interim Participant Contact Source Document	IE06 Treatment Phase Phone Contact

5.3 Baseline 0B Visit (500 mg treatment group only)

Window: Within 14 days of Baseline 0A Visit, +/- 3 days

Time Point	Description of Procedure	Source Document	eCRFs
Pre visit	Review visit checklist and ensure site is prepared for visit (procedures, etc.).	NA	NA
At Visit	Collect participant's interim medical history	Baseline 0B Visit Source Document	NA
At Visit	Ask the participant about any changes in medications 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)	Baseline 0B Visit Source Document	Adverse Events
At Visit	Measure pre-dose glucose via clinic meter. Do not administer study drug dose if result is < 50 mg/dl	Baseline 0B Visit Source Document	IE04 Study Drug Form
At Visit	Specimen Collection: 1. Pre Dose Specimens	Signed and dated printout of specimen collection form	Baseline 0B Specimen Collection
At Visit	Administer study drug dose to participant	Baseline 0B Visit Source Document	IE04 Study Drug Form
At Visit	Observe participant for two hours post study drug dose	Baseline 0B Visit Source Document	IE04 Study Drug Form
At Visit	Specimen collection: 1. Post Dose Specimens	Signed and dated printout of specimen collection form	Baseline 0B Specimen Collection
Post Visit	Enter data collected on source documents into the eCRFs online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the SMS Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions	NA	NA

	on use of the electronic shipping system.		
Post Visit	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.4 Month 1 Visit

Window: 30 days from Baseline, +/- 3 days

Time Point	Description of Procedure	Source Document	eCRFs
Pre visit	Contact participant to remind them to withhold study drug dose on visit date to be administered in clinic (67.5mg only)	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	Month 1 Source Document	IE02 Study Visit Form
At Visit	Ask the participant about any changes in medications 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)	Adverse Events	Adverse Events
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Month 1 Source Document	IE02 Study Visit Form
At Visit	Measure pre-dose glucose via clinic meter. Do not administer study drug dose if result is < 50 mg/dl	Month 1 Visit Source Document	IE04 Study Drug Form
At Visit	Specimen Collection: 1. Pre Dose Specimens	Signed and dated printout of specimen collection form	Month 1 Specimen Collection
At Visit	Administer study drug dose to participant	Month 1 Visit Source Document	IE04 Study Drug Form
At Visit	Observe participant for two hours post study drug dose	Month 1 Visit Source Document	IE04 Study Drug Form
At Visit	Specimen collection: 1. Post Dose Specimens 2. CBC with differential 3. Mechanistic Assessments a. Whole Blood – PBMC/Plasma b. Whole Blood – RNA c. Serum – Mechanistic Serum	Signed and dated printout of specimen collection form	Month 1 Specimen Collection
At Visit	Collect returned study drug and calculate	Month 1	IE04 Study

	compliance, if applicable	Source Document	Drug Form
At Visit	Dispense study drug	Month 1 Source Document	IE04 Study Drug Form
Post Visit	Enter data collected on source documents into the eCRF'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
Post Visit	Perform the treatment phase phone contact every 14 days between visits	Interim Participant Contact Source Document	IE06 Treatment Phase Phone Contact

5.5 Month 2 Visit

Window: 60 days from Baseline, +/- 7 days

Time Point	Description of Procedure	Source Document	eCRFs
Pre visit	Review visit checklist and ensure site is prepared for visit (procedures, etc.).	NA	NA
At Visit	Collect participant's interim medical history	Month 2 Source Document	IE02 Study Visit Form
At Visit	Ask the participant about any changes in medications 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)	Adverse Events	Adverse Events
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Month 2 Source Document	IE02 Study Visit Form
At Visit	Specimen collection: <ol style="list-style-type: none"> 1. CBC with differential 2. Mechanistic Assessments <ol style="list-style-type: none"> a. Whole Blood – PBMC/Plasma b. Whole Blood – RNA c. Serum – Mechanistic Serum 	Signed and dated printout of specimen collection form	Month 2 Specimen Collection
At Visit	Collect returned study drug and calculate compliance	Month 2 Source Document	IE04 Study Drug Form

At Visit	Dispense study drug	Month 2 Source Document	IE04 Study Drug Form
Post Visit	Enter data collected on source documents into the eCRF'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
Post Visit	Perform the treatment phase phone contact every 14 days between visits	Interim Participant Contact Source Document	IE06 Treatment Phase Phone Contact

5.6 Month 3 Visit

Window: 90 days from Baseline, +/- 7 days

Time Point	Description of Procedure	Source Document	eCRFs
Pre visit	Review visit checklist and ensure site is prepared for visit (procedures, etc.).	NA	NA
At Visit	Collect participant's interim medical history	Month 3 Source Document	IE02 Study Visit Form
At Visit	Ask the participant about any changes in medications 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)	Adverse Events	Adverse Events
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Month 3 Source Document	IE02 Study Visit Form
At Visit	Specimen collection: <ol style="list-style-type: none"> 1. CBC with differential 2. HbA1c 3. Mechanistic Assessments <ol style="list-style-type: none"> a. Whole Blood – PBMC/Plasma b. Whole Blood – RNA c. DNA (for ages ≥ 3 to < 18 years, weight 21 - 24 kg, collect DNA at Month 6 instead of this visit. Refer to Blood Volume Table for more information) 	Signed and dated printout of specimen collection form	Month 3 Specimen Collection

d. Serum – Mechanistic Serum			
At Visit	Collect returned study drug and calculate compliance	Month 3 Source Document	IE04 Study Drug Form
At Visit	Dispense study drug	Month 3 Source Document	IE04 Study Drug Form
Post Visit	Enter data collected on source documents into the eCRFs 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
Post Visit	Perform the treatment phase phone contact every 14 days between visits	Interim Participant Contact Source Document	IE06 Treatment Phase Phone Contact

5.7 Month 6 Visit

Window: 180 days from Baseline, +/- 7 days

Time Point	Description of Procedure	Source Document	eCRFs
Pre visit	Review visit checklist and ensure site is prepared for visit (procedures, etc.).	NA	NA
At Visit	Collect participant's interim medical history	Month 6 Source Document	IE02 Study Visit Form
At Visit	Ask the participant about any changes in medications 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)	Adverse Events	Adverse Events
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Month 6 Source Document	IE02 Study Visit Form
At Visit	Conduct a 2-hour OGTT	Local OGTT Source	Month 6 Specimen Collection
At Visit	Specimen collection: 1. OGTT 2. CBC with differential	Signed and dated printout of specimen	Month 6 Specimen Collection

	3. HbA1c 4. Mechanistic Assessments <ol style="list-style-type: none"> a. Whole Blood – PBMC/Plasma b. Whole Blood – RNA c. DNA (<i>for ages ≥ 3 to < 18 years, weight 21 - 24 kg, collect DNA at this visit instead of Month 3. Refer to Blood Volume Table for more information</i>) d. Serum – Mechanistic Serum 	collection form	
At Visit	Collect returned study drug and calculate compliance	Month 6 Source Document	IE04 Study Drug Form
Post Visit	Enter data collected on source documents into the eCRFs online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s).	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.8 Month 7 Visit

Window: 210 days from Baseline, +/- 7 days

Time Point	Description of Procedure	Source Document	eCRFs
Pre visit	Review visit checklist and ensure site is prepared for visit (procedures, etc.).	NA	NA
At Visit	Collect participant's interim medical history	Month 7 Source Document	IE02 Study Visit Form
At Visit	Ask the participant about any changes in medications 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)	Adverse Events	Adverse Events
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Month 7 Source Document	IE02 Study Visit Form
At Visit	Specimen collection: <ol style="list-style-type: none"> 1. CBC with differential 2. Mechanistic Assessments <ol style="list-style-type: none"> a. Whole Blood – PBMC/Plasma b. Whole Blood – RNA 	Signed and dated printout of specimen collection form	Month 7 Specimen Collection

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

5.9 Month 8 Visit

Window: 240 days from Baseline, +/- 7 days

Time Point	Description of Procedure	Source Document	eCRFs
Pre visit	Review visit checklist and ensure site is prepared for visit (procedures, etc.).	NA	NA
At Visit	Collect participant's interim medical history	Month 8 Source Document	IE02 Study Visit Form
At Visit	Ask the participant about any changes in medications 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)	Adverse Events	Adverse Events
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Month 8 Source Document	IE02 Study Visit Form
At Visit	Specimen collection: <ol style="list-style-type: none"> 1. CBC with differential 2. Mechanistic Assessments <ol style="list-style-type: none"> a. Whole Blood – PBMC/Plasma b. Whole Blood – RNA c. Serum – Mechanistic Serum 	Signed and dated printout of specimen collection form	Month 8 Specimen Collection
Post Visit	Enter data collected on source documents into the eCRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s).	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.10 Month 9 Visit

Window: 270 days from Baseline, +/- 7 days

Time Point	Description of Procedure	Source Document	eCRFs
Pre visit	Review visit checklist and ensure site is prepared for visit (procedures, etc.).	NA	NA
At Visit	Collect participant's interim medical history	Month 9 Source Document	IE02 Study Visit Form
At Visit	Ask the participant about any changes in medications 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)	Adverse Events	Adverse Events
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Month 9 Source Document	IE02 Study Visit Form
At Visit	Specimen collection: <ol style="list-style-type: none"> 1. CBC with differential 2. HbA1c 3. Mechanistic Assessments <ol style="list-style-type: none"> a. Whole Blood – PBMC/Plasma b. Whole Blood – RNA c. Serum – Mechanistic Serum 	Signed and dated printout of specimen collection form	Month 9 Specimen Collection
Post Visit	Enter data collected on source documents into the eCRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s).	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.11 Month 12 Visit

Window: 360 days from Baseline, +/- 14 days

Time Point	Description of Procedure	Source Document	eCRFs
Pre visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc.). Refer to instructions above for location of visit checklists.	NA	NA
Pre visit	Remind the participant that they need to be fasting for this visit.	NA	NA
At Visit	Collect participant's interim medical history	Month 12 Source Document	IE02 Study Visit Form
At Visit	Ask the participant about any changes in medications since the last visit.	ConMeds	Concomitant Medication
At Visit	Conduct a physical exam	Month 12 Source Document	IE02 Study Visit Form
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Month 12 Source Document	IE02 Study Visit Form
At Visit	Conduct a 2-hour OGTT	Local OGTT Source	Month 12 Specimen Collection
At Visit	Specimen collection: <ol style="list-style-type: none"> 1. CBC with differential 2. OGTT 3. HbA1c 4. Mechanistic Assessments <ol style="list-style-type: none"> a. Whole Blood – PBMC/Plasma b. Whole Blood – RNA c. Serum – Mechanistic Serum 	Signed and dated printout of specimen collection form	Month 12 Specimen Collection CBC with Differential Form
Post Visit	Enter data collected on source documents into the eCRF's online. Please note, you must enter the Demographics eCRF in order for the correct OGTT collection time points to display on the Specimen Collection Form.	NA	NA
Post Visit**	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Reactivate subject in Pathway to Prevention	NA	NH07 – Change of Status

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
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5.12 Description of Study Procedures

5.12.1 Pregnancy Monitoring (All Visits)

If female of child-bearing potential, urine pregnancy tests are required at each visit. The test results and method of birth control (including abstinence) should be documented.

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

- Step 1. Contact the TNCC and notify them of the positive pregnancy test.
- Step 2. Conduct a confirmatory pregnancy test. (Note: **DO NOT** administer study drug or conduct an OGTT if the participant is confirmed pregnant).
- Step 3. Ask the participant if they would be willing to be followed on the study to record information about their pregnancy outcome.
 - a. If the participant does not want to be followed, withdraws consent, or becomes lost to follow up complete the “Change in Status” form. If the participant agrees to be followed,
 - i. At the end of the pregnancy, document the pregnancy outcome on the “Pregnancy Outcome” PRN eCRF.
 - 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 OGTT’s.
- Step 4. Place a note to file in the participant binder documenting the conversation and the outcome (i.e. participant agrees to be followed per study, participant does not agree to be followed per study, etc.).
- Step 5. Complete the “Pregnancy Confirmation” eCRF PRN form.
- Step 6. Fulfill any local reporting requirements (IRB, GCRC, etc.).

5.12.2 Study Drug Administration (Baseline 0A, Baseline 0B, Month 1, Month 2, Month 3)

All participants will receive active oral insulin capsules, supplied in either 67.5 mg to be taken daily, or a titrating dose up to 500 mg to be taken every other week. All subjects will be administered their study drug dose in clinic at visits Baseline 0A, Visit 0B (500 mg only), and Month 1. For participants randomized to daily treatment, the first blister cards are dispensed at Baseline 0A, and subsequent blister cards are dispensed at Month 1, Month 2 and Month 3 visits. For participants randomized to the every other week treatment, the first blister cards are

dispensed at Month 1, and subsequent blister cards are dispensed at visits Month 2 and Month 3. Study drug should be returned and compliance should be calculated at the Month 1, Month 2, Month 3 and Month 6 visits. Please reference the TN20 Pharmacy Manual of Operations for additional information.

5.13 Study Drug Monitoring

All participants randomized to treatment will be observed before and for two hours after their study drug dose at the Baseline 0A, Visit 0B (500 mg only), and Month 1 visits. The IV line should remain in place during the entire observation period, and should be discontinued at the conclusion of the observation period, upon discharge from the clinic.

Before the study drug dose is given at these visits, the participant should have their blood glucose level checked via a clinic meter. For blood glucose values < 50 mg/dl at Baseline 0A, the study drug dose should be withheld, the participant should be treated for hypoglycemia in accordance with clinic practices, and he or she should be withdrawn from the study.

If the participant's pre-dose glucose is < 50 mg/dl at Visit 0B or Month 1, the study drug dose should be withheld (and no further doses given); the participant should be treated for hypoglycemia in accordance with clinic practices, but he or she will continue with study visits per the schedule of assessments.

During the two hour observation period post dose, in addition to the 1 hour and 2 hour post dose sample collections, the participant should be monitored for any signs or symptoms of hypoglycemia, or other issues. Should the participant display signs of hypoglycemia, the blood glucose level should immediately be checked via clinic meter. If the meter blood glucose is < 50 mg/dl, the participant should be treated for hypoglycemia in accordance with clinic practices, and should remain in clinic under observation until the blood glucose returns to > 50 mg/dl.

Subjects with a meter blood glucose < 50 mg/dl post dose, will no longer receive study drug treatment, but should continue to be followed in the study per the schedule of assessments.

The TNCC should be contacted immediately in any case of a blood glucose meter value < 50 mg/dl.

5.14 End of Study Participation

5.14.1 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.

5.14.2 Participant Withdrawal or Lost to Follow Up

If it is determined that a participant has withdrawn or has been lost to follow up, the site should complete the "Change of Status" eCRF in the online EDC system.

1. The "Date change in status become effective" should reflect the date the participant withdrew or the date it was determined the participant was lost to follow up.
2. Proceed to section B, enter a date of withdrawal if appropriate and indicate the primary reason for withdrawal.

3. No further eCRF's or visits will be expected in the system for the participant.

If later the participant resumes participation on the trial the site should complete the "Change of Status" eCRF in the online EDC system and indicate the participant has rejoined the study.

1. The "Date change in status become effective" should reflect the date it was determined the participant rejoined the study
2. Proceed to section C, enter the date of the participant's first visit rejoining the study
3. The participant will rejoin the study according to the time point at which they would currently be if they had remained on the study (for example, if the participant left the study at month 3 and rejoined the study 3 months later, the next expected visit- and therefore procedures to follow- would be the 6 month visit).

5.14.3 Participant – Determining Lost to Follow Up

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

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

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

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

Note: No eCRF's need to be completed for this visit.

5.14.5 Onset of Diabetes

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

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

OR

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

OR

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

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

If a participant has an OGTT that indicates diabetes (clinical alert), the site should invite the participant for a repeat OGTT within 60 days. In order to make a diagnosis of diabetes, each of two consecutive OGTTs must meet diabetes criteria. Thus, if the second OGTT does not confirm the diagnosis, the participant will continue to be followed in the TN20 Immune Effects of Oral Insulin Study and will be asked to return for the next followup visit. At that time, the OGTT will be repeated and, if indicative of diabetes, will need to be performed a second time to confirm the diagnosis.

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

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

AND/OR

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

If a participant is diagnosed with T1D, the site should follow these procedures:

1. Complete the "Change in Study Status" eCRF PRN in the online electronic data capture system and indicate that the participant has developed type 1 diabetes and is inactive.
 - a. The "Date change in status became effective" should reflect the date the participant was diagnosed with type 1 diabetes.
 - b. Proceed to section B, enter a date of withdrawal and indicate the primary reason for withdrawal (development of T1D).
2. If the participant is within the Study Drug Administration Phase of the study (Visits # 0A, Baseline through Visit # 4, Month 6), the participant will no longer be able to continue with study drug administration. Please complete the TN20 Change in Study Drug eCRF and indicate the study drug has been discontinued.
 - a. The reason should be "development of T1D".
3. Complete the TN20 "Diabetes Onset Form" in the online electronic data capture system and indicate that the participant has developed diabetes.

The date of diagnosis will be defined as follows:

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

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

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

- b) For testing that cannot be done at a TrialNet Center or Affiliate, it is *strongly preferred* that the samples be collected and sent to the TrialNet Beta-Cell Function Laboratory for plasma glucose levels rather than relying on test results from the local (non-TrialNet) lab.
- c) The judgment about whether to perform an OGTT when there is concern that it will affect the participant's safety should be made by the Center Director or Affiliate investigator. [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), available data will be provided to the TNCC for review and adjudication by the TrialNet Diabetes Adjudication Committee.

Common scenarios with recommended actions are described below.

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. If this was to be the initial rather than confirmatory OGTT, the participant should be asked to return for a full OGTT.

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

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

Scenario 2:

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

Recommended Action: Follow the steps outlined in section 6.2.2 regarding the completion of visit procedures at an unapproved site.

Scenario 3:

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

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

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

Scenario 4:

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

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

Scenario 5:

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

Although routine self-monitoring of blood glucose is not recommended, it is possible that research participants will detect elevated blood glucose values based on home blood glucose testing as many participants have a family member with type 1 diabetes who tests regularly.

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

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

Scheduling Confirmatory OGTTs:

When a participant has an OGTT result that indicates diabetes (clinical alert), the site will receive an email notification from the TNCC and lab stating "Repeat OGTT requested. Follow your study protocol 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 participants to schedule a confirmatory test. It is important to explain to participants that these findings need to be confirmed before making a diagnosis of diabetes. In addition to temporary metabolic fluctuations due to illness or stress, there may be other reasons why an OGTT may need to be repeated (e.g. laboratory error, degradation of sample, shipping problems, etc.).

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

If the repeat OGTT indicates diabetes, the site will receive a second alert via email from the TNCC and the lab. At this time, the participant has met criteria for a diagnosis of diabetes (and has met study endpoint). Sites should complete the procedures outlined above (complete IE07 and IE08 forms). Coordinators should contact the TNCC Clinical Research Administrator if they have any questions.

5.14.6 Death

All deaths are considered serious adverse events and should be reported within 24 hours of notification, as this is an unexpected event for participants in the TN20 Study. Site coordinators should follow these procedures:

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

5.15 Missed Visits/Visits Occurring Outside Window

5.15.1 Missed Visit

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

1. For that visit time point, under “Tracking” select “Not Done” for all forms and indicate the reason the visit was not completed within the allowable window.
2. Document the reason for the missed visit in the source.
3. Complete one IE13 Protocol Deviation Form indicating that the visit was missed.

5.15.2 Visit Occurs Outside of Allowed Window

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

1. For that visit time point, complete the visit eCRFs using the correct visit forms (For example, if Visit 5 occurred 5 days after the allowable window, the visit will still be entered onto the Visit 5 visit forms).
2. Complete one Protocol Deviation form indicating that the visit and samples were collected outside of the allowable visit window.

6. INSTRUCTIONS FOR PARTICIPANT TRANSFER AND REMOTE STUDY VISITS

6.1 Participant Transfer

6.1.1 Originating Site Procedures

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

- Step 1. Contact the TNCC and notify them of the proposed participant transfer.
- Step 2. Determine the most suitable new site for the participant.
- Step 3. Provide the participant with contact information for the new site. Inform the participant that they will need to contact the new site's main contact within 7 days.
- Step 4. Contact the new site's main contact ASAP and inform them that a participant from your site will be transferring to them soon. You can provide information about where the participant is (time point) in the study. You CANNOT provide any PHI to the new site until after the participant signs a HIPAA authorization and all other required forms at the new site.
- Step 5. Review all data and eCRFs; complete and enter all missing data and attempt to reconcile any missing or outstanding tests results/source documents.
- Step 6. Notify the originating site pharmacy of the transfer if the participant has not completed the course of treatment. The originating site should contact the TNCC for additional steps regarding transfer of study agent.
- Step 7. Once all data has been entered/reconciled and the participant has signed the new site's HIPAA authorizations, the originating site should navigate to the PRN form "Permanent Participant Site Transfer" and transfer the participant to the new site. See section 9.4 for instructions on how to access PRN forms.
- Step 8. Notify the new site that the participant has been transferred in the online system.

6.1.2 New Site Procedures

- Step 1. Once the originating site has made contact, wait for a call or email from the participant. If the participant has not made contact within 7 days, contact the originating site for direction.
- Step 2. Once the participant has made contact, schedule the participant for a visit or mail the new site consent forms and HIPAA authorizations to the participant for their review.
- Step 3. If the participant wishes to continue participation at the new site, bring the participant to the new site to sign the consent forms and HIPAA authorizations.

- Step 4. The new site should notify the originating site when the participant has signed the consent forms and HIPAA authorizations.
- Step 5. The originating site will notify the new site when participant has been transferred in the online system.

6.1.3 Procedures for Data Correction After Transfer

If the originating site needs to correct any data in the system after the participant has been transferred they will be able to access the participant record for data correction purposes only, and will not need to transfer the record back to the originating site. The originating site will only be able to access the participant’s electronic record if the participant had been seen previously at the site.

The originating site should access the participant’s record by entering the participant’s PID number under the “Find a Participant” page. Please note: The originating site will only be able to view the participant’s record by searching with a specific PID number. The participant will not show up under the site list of the participant’s originating site location and will only show up under the site list of the participant’s currently visited 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 (other than remote specimen collection procedures) can be performed at an unapproved site.

6.2.2 Collecting Specimens at an Unapproved Site

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

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

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

Procedures:

- Step 1. The unapproved site needs to be currently approved by TrialNet for at least one TrialNet protocol. This approval must be on file at the TNCC OR be a lab vendor.
- Step 2. The unapproved site only conducts procedures that they already conduct under the approval of another TrialNet protocol or for which they have appropriate training/resources already in place.
- Step 3. The unapproved site **will not use** any of the online specimen collection forms for the visit.

- a. The unapproved site should use its own source documents for the visit.
- Step 4. The unapproved site **will not use** the online Specimen Management System (SMS).
- Step 5. The site may choose to use its own supplies to collect specimens or may request a study kit per its Clinical Center's current procedure.
- Step 6. Upon completion of the study visit, the unapproved site will send *all* samples collected and source documents via FedEx to the enrolling site immediately.
- Step 7. The enrolling site will enter the visit online using online specimen collection forms, etc. and use the online specimen shipment system to ship specimens to the proper lab.

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

7. INFORMED CONSENT

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

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

7.1 *Required Elements of Informed Consent*

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

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
2. A description of any reasonably foreseeable risks or discomforts to the participant.
3. A description of any benefits to the participant 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 participant.

5. A statement describing the extent, if any, to which confidentiality of records identifying the participant 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 participants' rights, and whom to contact in the event of a research-related injury to the participant.
8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and that the participant may discontinue participation at any time without penalty or loss of benefits to which the participant 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 participant:

1. A statement that the particular treatment or procedure may involve risks to the participant (or to the embryo or fetus, if the participant 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 participant's consent.
3. Any additional costs to the participant that may result from participation in the research.
4. The consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the participant.
5. A statement that significant new findings developed during the course of the research which may relate to the participant's willingness to continue participation will be provided to the participant.
6. The approximate number of participants involved in the study.

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 participant 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.

7.1.1 Assent of Children

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

7.2 Informed Consent Process

7.2.1 Administration of the Informed Consent Process

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

Informed consent should be obtained from each research participant 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 participant/representative should enter the date of signature on the consent document, to permit verification that consent was actually obtained before the participant began participation in the study. If consent is obtained the same day as a study procedure, the participant'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 participant and the original signed consent document should be retained in the study records.

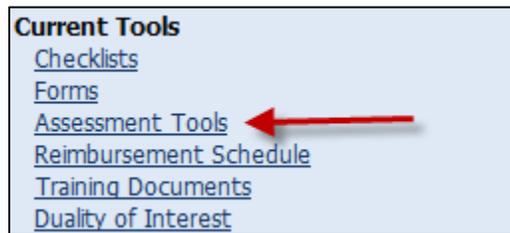
Source: <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126431.htm>

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 participant 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 TN20 protocol home page under Assessment Tools:



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

- All of the participant’s questions were answered/concerns addressed.
- Participant was given time to review the consent form and to discuss participation in this study with family members/others.
- The participant 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 participant.
- Privacy was maintained throughout the informed consent process.
- A copy of the consent form was given to the participant.

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. For TN20, the PID will remain the same as the participant’s PID under TN01.

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 participant data entered by each user's site; in this way only the consenting site may view data for their participants

User Name and Password: A username and password will be issued to all personnel by the TNCC. All individuals issued a password must be identified as a qualified person (appropriate human subjects training, ethic's board approval for specific role, etc) by each site's Principal Investigator on a continuously maintained site delegation log (site delegation of authority log). The user will be required to change the standard password the first time he or she logs into the system. All users are instructed to keep their login and password secure and are not allowed to share their username and password.

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

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

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

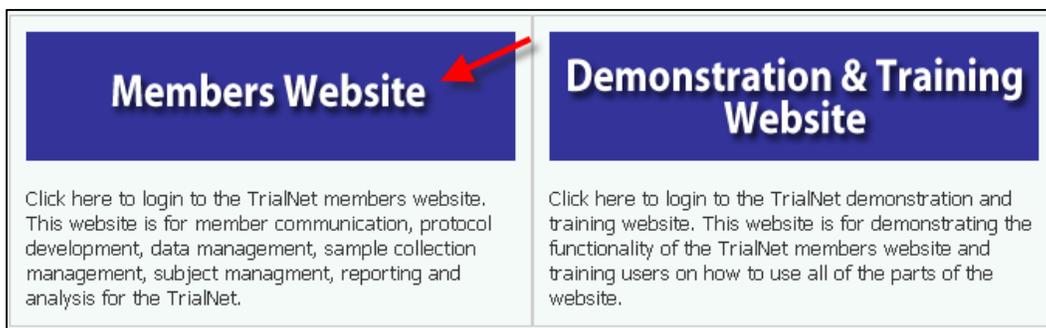
Registration of participants on this protocol employs an interactive data system in which the clinical site will attest to the participant's eligibility as per protocol criteria and that an appropriate informed consent has been obtained. Ethic's board/IRB approval for the protocol must be on file at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

9. ONLINE DATA CAPTURE SYSTEM

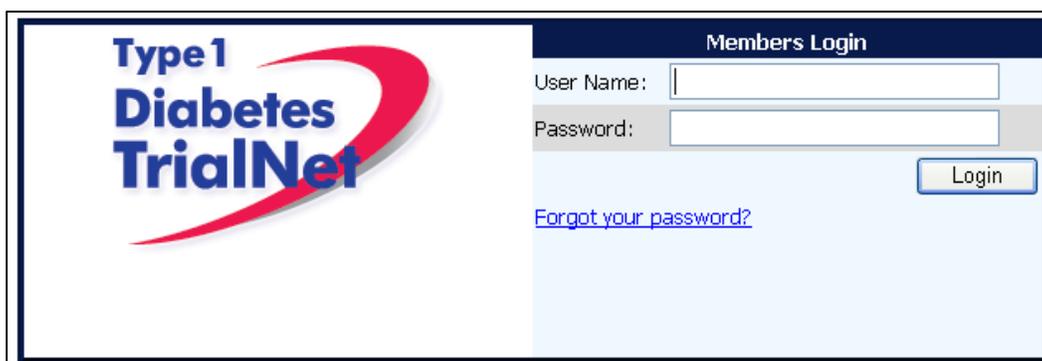
9.1 Overview and Basic Functionality

9.1.1 Login/Navigate to the TN20 Protocol Manager Area

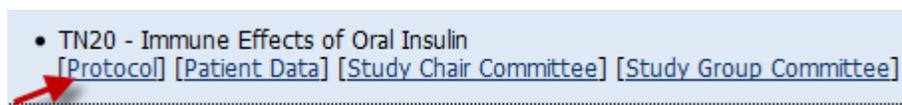
Step 1. Procedure to login and navigate to the TN20 protocol manager area: Log into TrialNet Members Site: <http://www.diabetestrialnet.org/members.htm>.



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



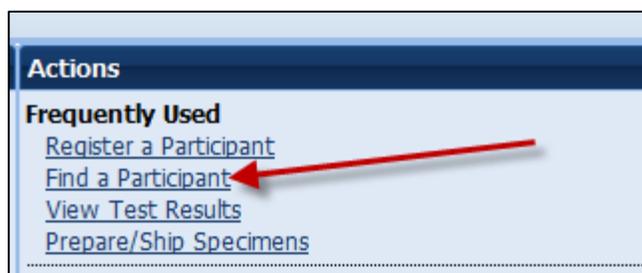
Step 3. Navigate to the “Protocols” portlet. Under TN20, select “Protocol.”



9.1.2 Finding a Participant

Note: This procedure will be done for every visit.

Step 1. Procedure to find participant: Once in TN20 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 participants matching entered criteria will populate below the search box. Click on Local ID (in blue text color). This will open the Participant Detail Screen

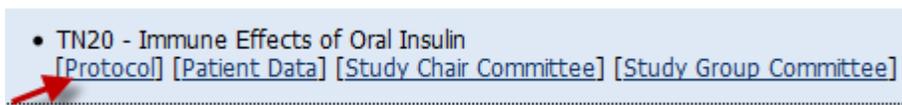
Local ID	Participant ID	Letters	Study Site	Registration Date	Participant Status
1202020202	100309	DEM	12 - University of Texas [12]	20 Mar 2009	Registered
120900086	100301	ABC	12 - University of Texas [12]	09 Mar 2009	Eligible
081201	100295	tnm	12 - University of Texas [12]	05 Mar 2009	Eligible
2009022401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

page 1 of 1 Total Records: 4

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9.1.3 Registering a Participant

Step 1. Log into TrialNet Members Website and navigate to the Protocols portlet. Select the “Protocol” link under TN20 –Immune Effects of Oral Insulin



Step 2. Once in TN20 Home Page, navigate to the Actions portlet and select “Register Participant.”



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

- a. Local ID: The site can enter the desired local ID for the participant. This can include numbers and letters.
- b. Letters: Enter three letters.
- c. Participant ID: Enter PID as assigned in the TN01 Pathway to Prevention Study
- d. Site: Select applicable site.

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

The image shows a screenshot of the 'Register a Participant' form. The form has four main input fields: 'Local ID:*', 'Letters:*', 'Participant ID:', and 'Site:'. There are yellow callouts with red arrows pointing to each field: 'Site creates Local ID' points to the Local ID field, 'Any three letter code assigned by the site to identify an individual' points to the Letters field, 'Click arrow to select your site' points to the Site dropdown menu, and 'Select after entering Local ID, Letters and Site' points to the 'Register Participant' button. The form also includes a 'Participant ID:' field with a note: '(Enter only if you wish to register a participant that has already been registered on a different protocol.)'.

You have successfully registered Participant ID : 100308

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

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

The image shows a screenshot of the 'Register a Participant' form with the following fields filled out: 'Local ID:*' is 2009030101, 'Letters:*' is ABC, and 'Site:' is University of Miami [6]. The 'Participant ID:' field is empty. A yellow callout box at the bottom left contains the text 'You have successfully registered Participant ID : 100308'. The 'Participant Details' button is highlighted in yellow, and the 'Register Participant' button is visible to its right. A large 'DEMO' watermark is overlaid on the form.

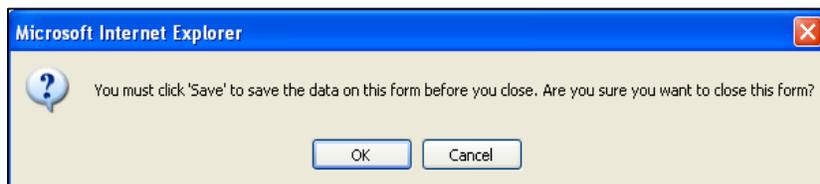
9.1.4 Save and Close eCRFs

Note: This procedure will be the same after each eCRF is completed.

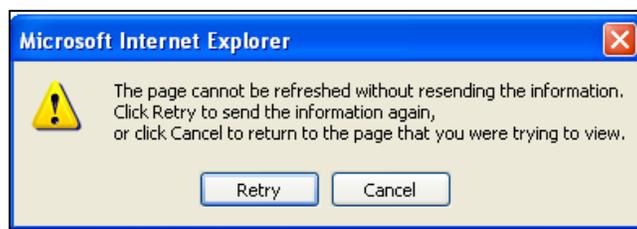
Step 1. Procedure to save and close-out form: After entering the data select “Save”. The message “Forms saved successfully” will display.



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.

The screenshot shows the 'Main Collection' tab in the TrialNet Specimen Management System. At the top, there are buttons for 'Save All', 'Show Instructions', 'Print', 'Collect QC', 'Prepare Specimen Shipment', 'Browse Specimens', 'Clear Group', and 'Close'. Below these are input fields for 'Scanner' and 'Keyboard'. A table lists specimens with columns for 'Test Name', 'Barcode', 'Reserved', 'Date of Draw', 'Not Collected', 'Not Required', 'Priority', and a status icon. Two specimens are listed: 'Serum - autoantibodies' (Barcode: TNSSS1, Date: 20 Nov 2009) and 'Serum - chemistries' (Barcode: TNSSS2, Date: 20 Nov 2009). Red arrows point to the 'Save All' button and the 'Close' button.

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

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 Interviewer User ID (required on every form in order to save a form).

The screenshot shows two form fields. The first is 'Date of Visit:' with a red asterisk and a red arrow pointing to it. The input field contains '6', a dropdown menu set to 'Mar', and '2009', followed by a 'Date' link. The second is 'Interviewer User ID:' with a red asterisk and a red arrow pointing to it. The input field contains '54491'.

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

NOTE: Interviewer User ID indicates the staff member who collected the data (which may differ from the one inputting the data).

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

The legend box contains two lines of text: '* These fields are required in order to SAVE the form' (in red) and '* These fields are required in order to COMPLETE the form' (in blue).

9.1.7 Clear ALL Data from a Form

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

- Step 1. Navigate to the form which you would like to clear.
- Step 2. Click on the button entitled "Clear Form" in the upper right hand corner of the screen.

Protocol # TN20 - TN20 Immune Effects of Oral Insulin Clear Form

Participant ID:	106185	Date of Registration:	12 Nov 2015
Local ID:	TEST123	Letters:	TES
Status:	Not Eligible	Date of Baseline Exam:	12 Nov 2015
Site:			

IMMUNE EFFECTS OF ORAL INSULIN TRIAL INITIAL VISIT FORM

Page: 1 of 3

* These fields are required in order to SAVE the form

* These fields are required in order to COMPLETE the form

Date of Visit: * 12 Nov 2015 [Date](#)

Interviewer User ID: * 56290

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."

Clear Form Data	
Form Name:	TN20_InitialVisit
Form Cd:	212475
History Type:	Subject History
History Id:	1569941
<input type="button" value="Clear"/> <input type="button" value="Cancel"/> <input type="button" value="Close"/>	

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."

Are you sure you want to clear the form's data and associated event?

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

Clear Form Data

Form Name: TN20_InitialVisit

Form Cd: 212475

History Type: Subject History

History Id: 1569941

Clear Cancel Close **Form data cleared successfully.**

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

9.1.8 Clear ALL Data from a Collection Form

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

9.2 Participant Details

Timepoint	Event Title
Initial Visit	Registration Form
	IE01 Initial Visit Form
	Concomitant Medications
	CBC with Differential Form
	Screening Specimen Collection
Baseline 0A	IE03 Baseline Eligibility Form
	IE02 Study Visit Form
	CBC with Differential Form
	IE04 Study Drug Form
	Baseline 0A Specimen Collection
	Treatment Start Date

- Time Point – When this event occurs in the timeline that starts at registration (e.g. Initial Visit, Baseline 0A, Baseline 0B Month 1, etc)
- Event Title – Title of the Event/Form (e.g. Demographics, Initial Visit, Concomitant Medications, etc)
- Tracking – The Event Tracking Form. This form should be completed if a visit was missed

The screenshot shows the 'Event Tracking Form' for the event 'Screening Visit Start Date' at the 'Screening' time point. A red arrow points to the 'Not done' radio button under the 'Event Done?*' field. A red asterisk note states: '* These fields are required in order to SAVE the form'. Below this, the 'Why wasn't this done?' section contains several checkboxes: Participant missed appointment, Participant/parent refused, Unable to obtain sample, Unable to contact subject, Illness, and Other. At the bottom, there are 'Submit', 'Clear', and 'Close' buttons. The 'Submit' button is highlighted in yellow.

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

9.3 Visit Forms

9.3.1 Data Entry for All Visit Forms

The visit forms that are currently within window will be highlighted yellow on the Participant Details Page. Data should only be entered into the forms for the highlighted visit. No visit data should be entered into PRN forms unless it is a true PRN visit, outside of the regularly scheduled visits per the protocol and Schedule of Assessments.

- Step 1. Be sure the Source Document is completed prior to completing forms
- Step 2. Under Event Title select the form you want to open.

Timepoint	Event Title	Tracking	Due Date	Last Modified Date	Event Status
Initial Visit	Registration Form		12 Nov 2015	12 Nov 2015	Complete
	IE01 Initial Visit Form	Tracking			
	Concomitant Medications	Tracking			
	CBC with Differential Form	Tracking			

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

Step 4. Complete all sections of the form

Step 5. After entering data, please reference section 9.1.4 Save and Close eCRF form.

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

9.3.2 Concomitant Medications

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

Step 2. Complete all sections for each medication listed.

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

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

Protocol # TN20 - TN20 Immune Effects of Oral Insulin

Participant ID: 363643	Date of Registration: 12 Nov 2015
Local ID: dmq-001	Letters: DMQ
Status: Registered	Date of Baseline Exam: 12 Nov 2015
Site: USF Diabetes Center [1265]	

Concomitant Medications

* These fields are required in order to SAVE the form
 * These fields are required in order to COMPLETE the form

Date of Initial Assessment: * Date **Enter Date of Visit**

Interviewer User ID: * **Enter User ID**

Assessment Date	Medication	Dose	Units	Frequency	Interval	Route	Indication	Start Date	Continuing?	Stop Date
<input type="text"/>	<input type="radio"/> Yes <input type="radio"/> No	<input type="text"/>								

Add

Save Print Close Window

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 and mechanistic samples. Tolerance collections include OGTTs.

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

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

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

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

9.3.5 Specimen Collection Form: Mechanistic Collections

Mechanistic collections include Mechanistic Serum, PBMC, etc. If a mechanistic collection is required for a visit, a “Mechanistic” tab will appear in the specimen collection form for that visit.

Main Collection	Tolerance Collection	Mechanistic
Save All	Show Instructions	Print
Collect QC	Prepare Specimen Shipment	Browse Specimens

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

9.3.6 Baseline Eligibility Form

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

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

TN20 - TN20 Immune Effects of Oral Insulin			
Participant's Details			
Protocol # TN20 - TN20 Immune Effects of Oral Insulin			
Participant ID:	106185	Date of Registration:	12 Nov 2015
Local ID:	TEST123	Letters:	TES
Status:	Eligible	Date of Baseline Exam:	12 Nov 2015
Site:	USF Diabetes Center [1265]		

9.3.7 Participant Treatment Assignment

The ***Eligibility form must be complete*** and the participant must be eligible prior to assigning treatment to the participant. **For the TN20 protocol, randomization/treatment assignment should be completed at least one week prior to Baseline 0A.** Under the Actions portlet on the main protocol page select "Assign Treatment"

Actions
Frequently Used
Register a Participant
Find a Participant
View Test Results
Prepare/Ship Specimens
Participant Data
Register a Participant
Find a Participant
Assign Treatment
View Assigned Treatment Report

Step 1. A box will open titled Assign Treatment to Participant; enter both the Local ID and Participant ID.

Step 2. Select Assign Treatment.

- Step 3. 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 4. Print this screen as original source documentation of the assigned Randomization ID.
- Step 5. As applicable, contact the local site pharmacist (assigned on this study) and provide the pharmacist a copy of the treatment assignment screen print out, noting the Randomization ID.

9.3.8 Participant Treatment Assignment

9.4 PRN Forms

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

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

- Step 1. From the participant details page, on the left side of the main screen, above the study schedule, the PRN forms are located in the drop-down box entitled "Additional Study Forms/Events."
- Step 2. Select the form needed from the list.

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

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

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

Step 1. From the participant details page, on the right side of the main screen, directly beneath the participant 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.

IE10 Protocol Deviation Form Form List			
Protocol # TN20 - TN20 Immune Effects of Oral Insulin			
Participant ID:	106185	Date of Registration:	12 Nov 2015
Local ID:	TEST123	Letters:	TES
Status:	Not Eligible	Date of Baseline Exam:	12 Nov 2015
Site:	USF Diabetes Center [1265]		

Page: 1 of 1

Event date	Event Title
17 Nov 2015	IE10 Protocol Deviation Form

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

9.4.3 PRN Specimen Collection Forms

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

10. ADVERSE EVENT REPORTING PROCEDURES

All 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 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, with the exception of hypoglycemia and hyperglycemia, is the most current version of the Common Terminology Criteria for Adverse Events (CTCAE), 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 participant and/or may require medical or surgical intervention to prevent one of the outcomes listed above.

An adverse event is considered unexpected when the nature (specificity) or severity of the event is not consistent with the risks described in the protocol, investigator brochure, or informed consent document. 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), participant 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, with the exception of hypoglycemia and hyperglycemia, will come from the most current version of the Common Terminology Criteria for Adverse Events (CTCAE) developed and maintained by CTEP at National Cancer Institute. The CTCAE 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).

The CTCAE is organized broadly by System Organ Class (SOC) groupings. Each SOC is a broad classification of AEs based on anatomy and/or pathophysiology. Within each SOC, 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 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 Infection", listed in the Infections and Infestations Category, only has options for Grades 1-3.) The most severe grades are not appropriate for some AEs and therefore not included.

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)" 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://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.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 disorders SOC, arthritis is found under the Musculoskeletal and connective tissue disorders SOC.

There is an "Other" AE option for each SOC. This AE requires a description and should only be used when no other AE is applicable.

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 participant

-OR-

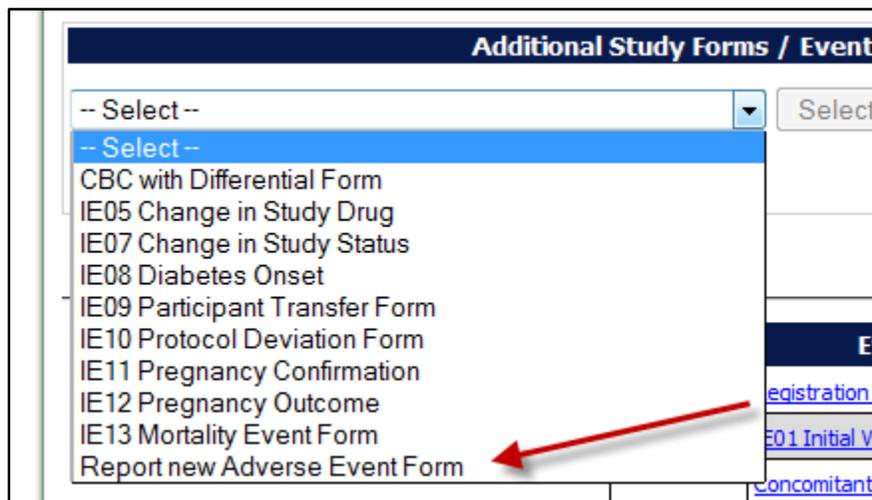
Is Unexpected/Unanticipated

Investigators must report all other SAEs within **5 working days** (of learning of the event). All other 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

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

You will be directed to an "Adverse Event Reporting Form". Complete this form to report an adverse event. The asterisked fields are required.

- a. To save this report, WITHOUT SUBMITTING, select "Save draft."
 - i. NOTE: This option does not submit the AE. To submit an Adverse Event you must select the "submit for review" option. "Save draft" allows you to re-open the form later and submit the event at a later time.
- b. To submit the report, click on "Submit for review."
 - i. NOTE: Selecting "submit for review" automatically saves the event as well.
- c. If the save is successful, you will see a success message. You may then close this window. If you do not see a success message, your report was not transmitted. Please resave, or contact your TNCC CRA immediately for assistance.

Adverse Event Reporting Form

Initial Report * These fields are required in order to SAVE the form

A. INTERVIEW INFORMATION

Adverse event report date (DD MMM YYYY) *

B. ADVERSE EVENT REPORT

Adverse event occurrence date (DD MMM YYYY) *

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

C. EVENT DESCRIPTION

Event Category *Help

Event Supra-term "Type of Event" *

Event Select "Site or Modifier" * (required only if options are present in drop down list)

Severity *

Event Details "Description"

Location of event treatment Other

D. EVENT ASSESSMENT

Expected Yes No *

Causality (by reporter) *

Was the adverse event associated with any of the following? (check all that apply)

- Development of a congenital anomaly or birth defect
- Development of a permanent, serious, disabling or incapacitating condition
- Death
- Hospitalization or prolonged hospitalization
- Life threatening
- Is another condition which investigators judge to represent significant hazards

Patient status (at time of report): *

Adverse event resolved date (DD MMM YYYY)

Date of death (DD MMM YYYY)

Additional comments

E. Study Drug Activity

Study Drug Start Date (DD MMM YYYY)	Study Drug Stop Date (DD MMM YYYY)
<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>

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

Did the event/reaction reappear after reintroduction? Yes No Not Applicable

F. CONCOMITANT MEDICATIONS

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

REPORTER INFORMATION

Reporter User ID

Details of Initial and Previous Follow-up Reports:

Adverse Event Reporting – Description of each field:

Section A. Interview Information:

Adverse event report date: This section refers to the date the site first learned of the event.

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. If an adverse event occurred before participant receives the first dose of study drug, the event should not be captured on AE form. Event should be captured on a Medical History Form and documented.

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

Is this a primary or secondary event?:

- o A **primary** AE is the main event.
- o A **secondary** AE is not a worsening or change in severity of the primary event, but it is an additional 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 resulted with a broken arm (secondary event).

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

Section C: Event Description

Event SOC: This refers to the body system that the AE falls under. There is a drop-down list of options, defined according to the CTCAE.

C. EVENT DESCRIPTION	
Event Category	*Help

Adverse Event: This refers to more specific description of the AE. There is a pre-populated drop-down list of the options. The drop-down list of options depends the SOC selected and is defined according to the CTACE.

Event Supra-term "Type of Event"	*
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 SOC and Adverse Event, as defined according to the CTCAE. *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 **participant** 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	<input checked="" type="radio"/> Yes <input type="radio"/> No * <input type="checkbox"/>

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

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

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

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

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

Patient status (at time of report):	▼ *
-------------------------------------	-----

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

Adverse event resolved date	▼	(DD MMM YYYY)
-----------------------------	---	---------------

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

Date of death	▼	(DD MMM YYYY)
---------------	---	---------------

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

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

Section E. Study Drug Activity:

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

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

E. Study Drug Activity	
Study Drug Start Date (DD MMM YYYY)	Study Drug Stop Date (DD MMM YYYY)
▼	▼
▼	▼
▼	▼
Add	

Did the Event/Reaction Abate after stopping drug?:

- a. Enter "Yes" if AE being reported resolved after treatment was stopped; or
- b. Enter "No" if AE being reported did NOT resolve after treatment was stopped; or
- c. Enter "Not Applicable" if the study drug was not stopped.

Did the event/reaction abate after stopping drug?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Not Applicable
---------------------------------------------------	-----------------------------------------------------------------------------------------

Did the event/reaction reappear after reintroduction?:

- 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.

Did the event/reaction reappear after reintroduction?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Not Applicable
-------------------------------------------------------	-----------------------------------------------------------------------------------------

Section F. Concomitant Medication:

As applicable, make sure any additional concomitant medications are listed in the concomitant medication running log.

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

Reporter Information:

Reporter User ID: User ID must be completed by person completing the AE Reporting Form.

REPORTER INFORMATION
Reporter User ID <input style="background-color: yellow;" type="text"/>

Form Disposition:

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

<input type="button" value="Save Draft"/> <input type="button" value="Submit for Review"/> <input type="button" value="Print"/> <input type="button" value="Close Window"/>

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 participant 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 the participant discontinued study treatment as expected per protocol. For instance: Participant 123456 discontinued study drug due to an AE, the **Stop Date** is the date the participant last took study drug.

E. Study Drug Activity					
Study Drug Start Date (DD MMM YYYY)			Study Drug Stop Date (DD MMM YYYY)		
12	Dec	2010	15	Jan	2011
<input type="button" value="Add"/>					

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 date when the participant resumed study drug. For instance: Participant 123456 resumed study drug, then the next **Start Date** entered would be the date study drug is resumed.

E. Study Drug Activity					
Study Drug Start Date (DD MMM YYYY)			Study Drug Stop Date (DD MMM YYYY)		
12	Dec	2010	15	Jan	2011
11	Apr	2011			
<input type="button" value="Add"/>					

**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:

Completed Additional Study Forms
Previous Adverse Event ←

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"

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

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

FOLLOW-UP INFORMATION	
Date of Follow-up	<input type="text"/> *
Reason for followup	<input type="text"/> *

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

Date of Follow-up	<input type="text"/> *
-------------------	------------------------

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

Reason for followup	<input type="text"/> *
<ul style="list-style-type: none"> Additional information requested by the medical monitor Correction of initial report New information, progression of event 	

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.

<input type="button" value="Save Draft"/>	<input type="button" value="Submit for Review"/>	<input type="button" value="Print"/>	<input type="button" value="Close Window"/>
-------------------------------------------	--------------------------------------------------	--------------------------------------	---------------------------------------------

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

10.5 Overview of Handling of Reported Adverse Events

The adverse events forms 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 to the TrialNet Medical Monitor. The TrialNet Medical Monitor will request further information, if necessary, confirm causality, and possibly recommend changes to the protocol or consent form as a consequence of the adverse event. Once reviewed, the Medical Monitor has the option 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.

10.6 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 of learning of the event.

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:

- 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. Site emails completed 3500A MedWatch report to TNCC CRA and TrialNet Medical Monitor (Brett J. Loechelt, MD; bloechelt@gmail.com)
- 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 participant (e.g., medical history, concomitant medications), administers the investigational drug, monitors the participant's response to the drug, is aware of the participant'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 participant 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.

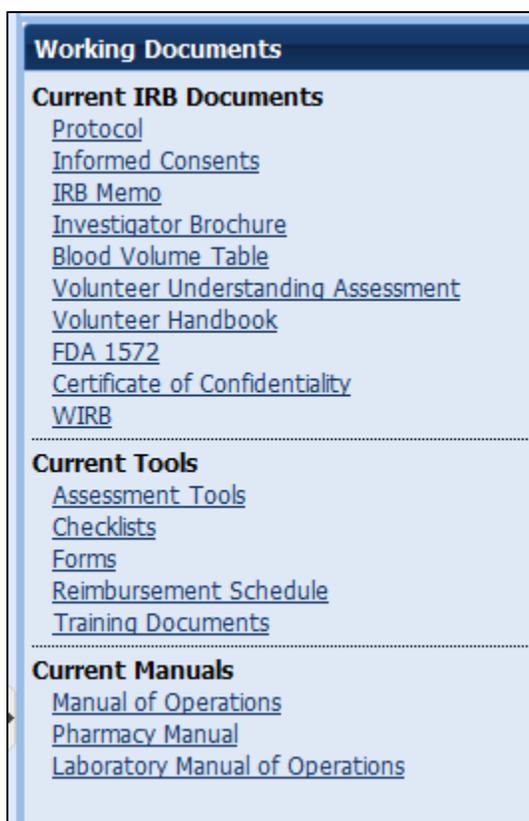
Source: FDA Draft Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies (September 2010).

11. PROTOCOL MANAGER: PORTLETS AND TOOLS

From the TN20 – Immune Effects of Oral Insulin homepage, there are a series of portlets meant to assist/aid sites in the conduct of the study.

11.1 TN20– Working Documents Portlet

From the TN20 – Immune Effects of Oral Insulin homepage, the latest protocol related documents, manuals, and other materials to aid sites in the conduct of the study are available in the “Working Documents” portlet.



Working Documents

Current IRB Documents

- [Protocol](#)
- [Informed Consents](#)
- [IRB Memo](#)
- [Investigator Brochure](#)
- [Blood Volume Table](#)
- [Volunteer Understanding Assessment](#)
- [Volunteer Handbook](#)
- [FDA 1572](#)
- [Certificate of Confidentiality](#)
- [WIRB](#)

Current Tools

- [Assessment Tools](#)
- [Checklists](#)
- [Forms](#)
- [Reimbursement Schedule](#)
- [Training Documents](#)

Current Manuals

- [Manual of Operations](#)
- [Pharmacy Manual](#)
- [Laboratory Manual of Operations](#)

11.1.1 Current IRB Documents

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

11.1.2 Current Tools

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

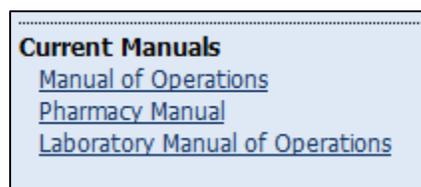
1. Checklists
 - a. Visit Checklists
2. Forms
 - a. Pharmacy Forms
 - b. Current Site Forms
 - c. Lab-related Forms
3. Assessment Tools
 - a. Template source documents
4. Reimbursement Schedule
5. Training Documents
 - a. Training Presentations and materials related to the study
 - b. Certification Quizzes.

11.1.3 Current Manuals

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

1. Manual of Operations (MOO)
 - a. Tracked and clean versions of the current MOO
 - b. Protocol specific appendices
2. Pharmacy Manual of Operations
 - a. Tracked and clean versions of the current Pharmacy MOO
3. Lab Manual
 - a. Current Lab MOO
 - b. Protocol specific appendices

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

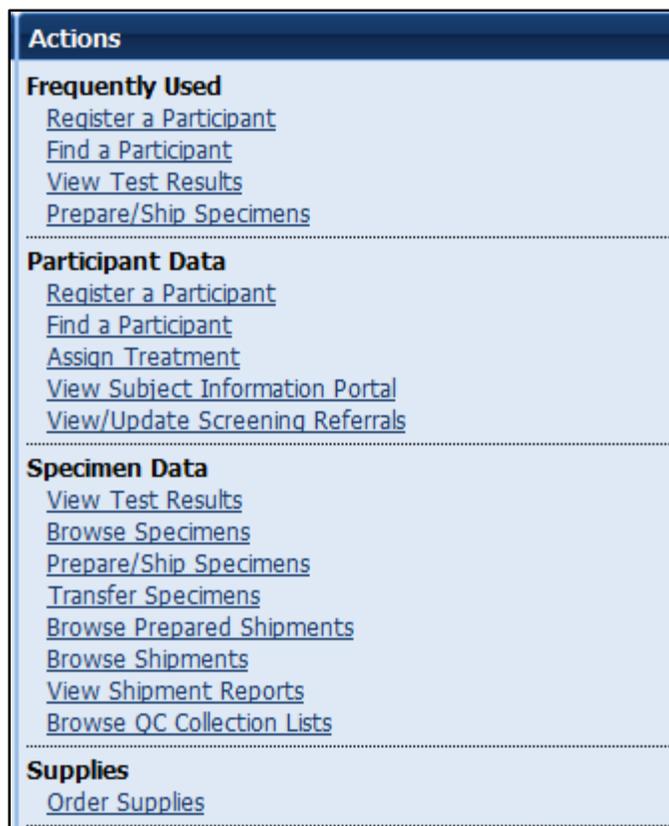


11.1.4 Archive

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

11.2 TN20 – Actions Portlet

From the TN20- Immune Effects of Oral Insulin homepage, all study-related actions are available in the “Actions” portlet.



11.2.1 TN20- 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 allows the user to register a new participant for the study.
2. Find a Participant
 - a. This link allows 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 allows the user to register a new participant for the study.

2. Find a Participant
 - a. This link allows 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.
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

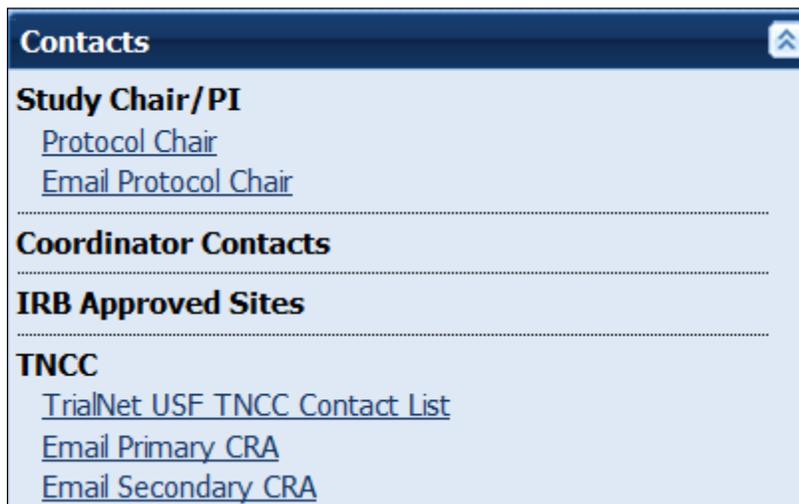
Under the “Specimen Data” actions header are links to the protocol actions that involve specimen shipment and reports.

11.2.4 Supplies

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

11.3 TN20 – Contacts

From the TN20- Immune Effects of Oral Insulin homepage, all study-related contacts are available in the “Contacts” portlet.



11.4 TN20 – Clinical Toolkit

From the TN20- Immune Effects of Oral Insulin homepage, all study-related clinical tools are available in the “Clinical Toolkit” portlet.

11.5 TN20– Calendar

From the TN20- Immune Effects of Oral Insulin homepage, all study-related calls, trainings and event are noted in the “Calendar” portlet.

TN20 - Immune Effects of Oral Insulin in EST	
Wed Nov 18 2015	
Thu Nov 19 2015	
Fri Nov 20 2015	
Sat Nov 21 2015	
Sun Nov 22 2015	
Mon Nov 23 2015	
Tue Nov 24 2015	
<input type="button" value="Monthly"/>	

11.6 TN20 Protocol Development Committee

From the TN20- Immune Effects of Oral Insulin homepage, links to the Protocol Chair Committee and Study Group Committee pages are located under the “Protocol Development Committee” portlet.

Protocol Development Committee 	
Protocol Chair Committee	
.....	
Study Group Committee	

In addition to the Protocol Chair Committee and Study Group Committee, there is a Joint Prevention Study Chair Committee and a CSG: Combined Study Working Group that incorporates all TrialNet prevention studies. These folders can be accessed from the main TrialNet homepage

Committees
Staff and Function Committees
Executive Committee
Joint Prevention Study Chair Committee
Center Directors
Trial Coordinators
International Trial Coordinators
Recruitment Coordinators
Affiliate Relations
Steering Committee
CSG: Combined Study Group
.....

11.7 TN20 – Publications

From the TN20 – Immune Effects of Oral Insulin homepage, all protocol specific publications, ancillary publications and data sharing policies are located under the “Publications” portlet.



11.8 TN20 – Frequently Asked Questions

From the TN20- Immune Effects of Oral Insulin homepage, all protocol specific frequently asked questions (FAQs) are located under the “Frequently Asked Questions” portlet.

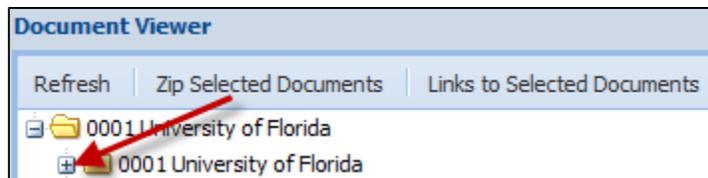
12. MEMBER’S WEBSITE REPORTS

12.1 eReg Binder Reports

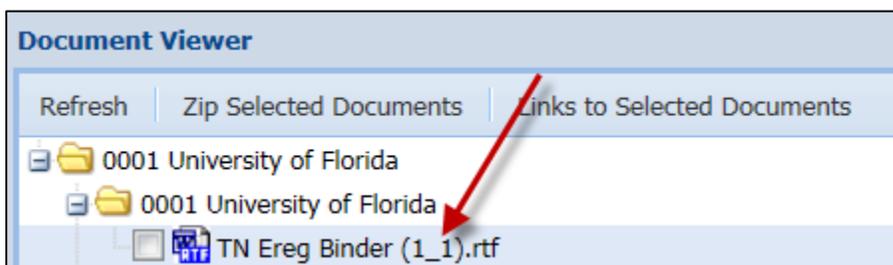
Step 1. Navigate to the “My Site” portlet which is located on the home page of the members website and select your clinical center link under EBinder Reports



Step 2. The document viewer will pop open. Click the (+) sign next to your site.



Step 3. The ‘TN eReg Binder rtf.’ file will populate. Double click the file to open the report. This report will include all documents currently uploaded to eReg for a specific site.



12.2 Network Wide Reports

Step 1. From the main TrialNet member’s homepage, navigate to the “Network Sites and Activities” portlet. Select the “Reports and Recruitment Activities” link.



Step 2. Select your site folder.

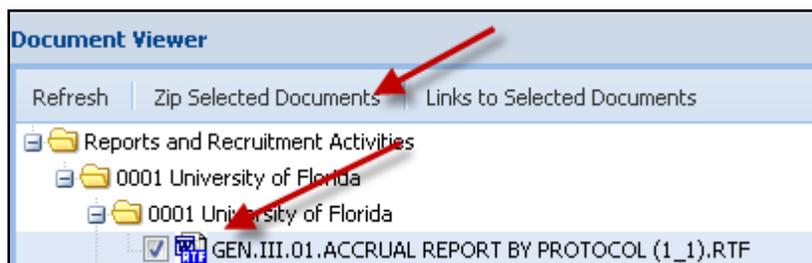
Step 3. Next, select the “General Reports” folder.

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

Network Wide Reports Currently Available:

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

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



12.3 Protocol Specific Reports

From the TN20 – Immune Effects of Oral Insulin homepage, all general and site specific reports are located under the “Reports and Recruitment” portlet.



12.3.1 Accessing Protocol Specific Reports

Step 1. To access reports with specific data for your individual site, from the TN20 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.

12.3.2 Protocol Specific Reports Currently Available:

Folder	Report Title	Report Description	Updated
General Reports	TN20.I.01.Accrual Report By Clinical Center.rtf	Accrual totals, by clinical center	Monthly
	TN20.I.02.Actual.v.Expected Accrual - Graph.rtf	Graph of actual verses expected accrual.	Monthly
	TN20.I.03.IRB Summary - Ethnicity, Race and Gender Report.rtf	IRB summary of ethnicity, race and gender for all participants	Monthly
	TN20.I.04.Adverse Event Summary Report.rtf	Summary of all reported AEs and SAEs	Weekly
	TN2001. Screening and Enrollment.rtf	Screening and Enrollment report by year	Weekly
Site Reports	TN20.II.01.Accrual Report By Institution (CC#).rtf	Accrual summary for clinical center and all affiliates	Monthly
	TN20.II.02.IRB Summary - Ethnicity, Race and Gender Report (CC#).rtf	IRB summary of ethnicity, race and gender for each site	Monthly
	TN20.III.01.Accrual Report (CC#_Site#).rtf	Displays protocol accrual totals	Monthly
	TN20.III.02.IRB Summary - Ethnicity, Race and Gender Report (CC#_Site#).rtf	Displays IRB summary of ethnicity, race and gender	Monthly
	TN20.III.03.Adverse Event Summary Report (CC#_Site#).rtf	Displays summary of all AEs and SAEs	Monthly
	TN20.III.09.Participant Schedule of Visits Report (CC#_Site #).rtf	Displays a calendar of target dates for participants' visits	Daily

13. SUPPLIES

13.1 Supply Ordering System Overview

All TrialNet supplies are ordered by sites through the Fisher BioServices online Supply Ordering System. This includes specimen collection, processing, and shipping supplies, barcode scanners, participant 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, TN01 teleforms, recruitment and retention materials, diabetes management supplies (if applicable).

The TNCC reviews and approves all orders placed in the Fisher online system within 48 hours and, if applicable, contacts TradeWinds to fulfill etched vial orders. For items provided by Fisher, the orders will be automatically fulfilled according to the date needed. Other supplies will be shipped directly from the USF TNCC upon order approval.

13.2 Ordering Supplies

13.2.1 Navigating the Fisher BioServices Supply Ordering System (SOS)

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

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



From the TN20 – Immune Effects of Oral Insulin Study homepage, navigate to the central “Actions” portlet and select “Order Supplies.”

Actions

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

Participant Data
[Register a Participant](#)
[Find a Participant](#)
[View Subject Information Portal](#)
[View/Update Screening Referrals](#)

Specimen Data
[View Test Results](#)
[Browse Specimens](#)
[Prepare/Ship Specimens](#)
[Browse Prepared Shipments](#)
[Browse Shipments](#)
[View Shipment Reports](#)
[Browse QC Collection Lists](#)

Supplies
[Order Supplies](#)

Adverse Events
[AE Admin](#)
[External AE Reporting](#)

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

Actions

Specimen Data
[View Test Results](#)
[Browse Specimens](#)
[Browse Shipments](#)
[Browse QC Collection Lists](#)

Supplies
[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.

User ID:

Password:

Login

Provided by Fisher BioServices

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

Add New Supply Order View All Supplies

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

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

Click to Display a Calendar

Proceed View Holiday Schedule for 2012 Cancel

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

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

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

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

Are you sure this is correct?

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

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

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

- b. If you do not have any special instructions or comments regarding the order, please select “Skip instructions/Comments Entry and Proceed to Supply Order.”

Order # 18476

Delete Order

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

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

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

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

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

1

Acknowledge Shipping Site Warning

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

OR

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

Acknowledge Shipping Site Warning

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

2

OR

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

Abandon/Delete Order

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

Finished Entering Items - Click Here to Continue

Sort by Site ID Ship-To: TNCC (S000PEC — Kelly Sadler)

Contact: [Kelly Sadler](#)

S000PEC - TNCC - Kelly Sadler

University of South Florida

USF Pediatrics Epidemiology Center

3650 Spectrum Blvd, Suite 100

Tampa, FL 33612 USA

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

Select a Protocol/Study	Select Assay
<div style="border: 1px solid gray; padding: 2px;"> Select a Protocol <div style="border: 1px solid gray; padding: 2px; margin-top: 2px;"> Select a Protocol General TN05 Anti-CD20 TN07 - Oral Ins (North American Sites) TN09 CTLA-4 Ig TN08 GAD New Onset TN07 - Oral Ins (International) TN14 Anti-IL1 Beta TN10 Anti-CD3 Prevention TN01 PTP Monitoring (International Sites) TN01 PTP Monitoring (North American Sites) TN01 PTP Screening (North American Sites) TN01 PTP Screening (International Sites) </div> </div>	<div style="border: 1px solid gray; padding: 2px;"> Select Assay </div>

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, PR incentive items, questionnaires, and shipping supplies.

Select a Protocol/Study	Select a Secondary Filter Criteria
<div style="border: 1px solid gray; padding: 2px;"> General </div>	<div style="border: 1px solid gray; padding: 2px;"> Select Assay <div style="border: 1px solid gray; padding: 2px; margin-top: 2px;"> Select Assay Clinical Supplies PBMC Isolation - Ficoll (TN07) PR Incentive Questionnaires Shipping </div> </div>

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

Select a Protocol/Study		Select Assay											
TN01 PTP Monitoring (North American Sites) ▼		Autoantibodies ▼											
Item #	Item Description	Part #	Catalog #	Supply Image	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	Click to view supply	Explain	50		0	0		USF	<input type="checkbox"/>	
PR-00199	2.5 mL Red Top Greiner SST Tube		Click to view Product Description	Click to view supply	Explain	50		0	0	31-Jul-2015	Fisher BioServices	<input type="checkbox"/>	

Step 10. Select the supplies you wish to order by placing a checkmark in the “Selected” column and indicating the number of units desired. Please note the packaging units per item when entering the number of units you require. Some items are packaged individually (Packaging Units = 1), while other supplies come in larger quantities. The “Total Quantity Ordered” field will update to reflect the total number of items that will be shipped.

For example, 1 unit of the 1.8 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 #	Supply Image	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	Click to view supply	Explain	50	2	100	0	1-Jan-1900	USF	<input checked="" type="checkbox"/>
PR 00199	2.5 mL Red Top Greiner SST Tube		Click to view Product Description	Click to view supply	Explain	50		0	0	31-Jul-2015	Fisher BioServices	<input type="checkbox"/>

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



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

ORDER FORM SUMMARY (ORDER NUMBER: 17400)

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

13.2.2 Supply Organization

Supplies are organized on the Fisher BioServices online Supply Ordering System (SOS) website by “Protocol/Study” and by “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 an “Assay” from the dropdown menus (see Section 13.2.1, Step 8).

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

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

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

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

The table below lists all filter criteria applicable to the TN20 – Immune Effects of Oral Insulin Study.

TN20 Immune Effects of Oral Insulin Supply Organization	
“Protocol” Filter Criteria	“Assay” Secondary Filter Criteria
TN20 Immune Effects (North American Sites)	Autoantibodies CBC Pre and Post Dose Samples DNA HbA1c Mechanistic Serum OGTT Whole Blood - PBMC/Plasma Whole Blood - RNA
TN20 Immune Effects (International Sites)	Autoantibodies CBC Pre and Post Dose Samples DNA HbA1c Mechanistic Serum OGTT Whole Blood - PBMC/Plasma Whole Blood - RNA
General Supplies	Clinical Shipping PR Incentive

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.

Laboratory References for Sites

[Specimen Processing References](#)

Specimen Management System

Specimen Data

[View Test Results](#)

[Browse Specimens](#)

[Browse QC Collection Lists](#)

Supplies

[Order Supplies](#)

[TN Supply Catalog](#) ←