



Protocol TN-19
Antithymocyte Globulin (ATG) and Pegylated
Granulocyte Colony Stimulating Factor (GCSF) in
New Onset Type 1 Diabetes

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

1.2 Current Protocol Synopsis (25JUL14)

Title	ATG-GCSF in New Onset Type 1 Diabetes
IND Sponsor	Type 1 Diabetes Trial Network (TrialNet)
Conducted By	Type 1 Diabetes Trial Network (TrialNet)
Protocol Chair	Michael J. Haller, MD
Accrual Objective	84
Study Design	Three-arm, 1:1:1 randomized, placebo controlled, double-blinded trial in which at least 28 subjects will receive active ATG-GCSF, at least 28 subjects will receive ATG alone and at least 28 subjects will receive placebo alone within 100 days from diagnosis of T1D. An adaptive design will be used to determine the variance of C-peptide over time and may require additional subjects to be enrolled in each group to preserve power.
Treatment Description	ATG will be administered at a dose of 2.5mg/kg as two divided IV infusions of 0.5mg/kg and 2mg/kg. GCSF will be administered at a dose of 6mg SC every two weeks for a total of 6 doses.

Study Duration	Enrollment is expected to occur over two-three years. Subjects will be followed up to 24 months from randomization in this protocol.
Objective	To determine the safety and ability of low dose ATG plus GCSF and low dose ATG alone to retain/enhance C-peptide production in new onset T1D patients demonstrating residual beta cell function.
Primary Outcome	The primary statistical hypothesis to be assessed in the study is whether the 2 hour area under the curve (change in baseline to 12 months) in residual beta cell function (C-peptide) will differ between those treated with ATG and GCSF or ATG alone as compared with placebo.
Secondary Goals	The study will also examine the effect of the proposed treatments on surrogate markers for immunologic and metabolic outcomes
Major Inclusion Criteria	Type 1 diabetes diagnosed within the past 100 days Age \geq 12 years < 46 At least one diabetes associated autoantibody

1.3 Study Contacts

TN19 ATG-GCSF Study TrialNet Coordinating Center (TNCC)		
USF TrialNet Coordinating Center (TNCC) University of South Florida Pediatrics Epidemiology Center Tampa, FL 33615	Primary Contact: Jessica Miller	Ph.: (813) 396-9543 Fax: 813-910-1233 Email: jessica.miller@epi.usf.edu
	Secondary Contact: Nichole Reed	Ph.: (813) 396-9461 Fax: 813-910-1245 Email: nichole.reed@epi.usf.edu

TN19 ATG-GCSF 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

TN19 ATG-GCSF Study Core Laboratories	
Please refer to the ATG-GCSF Laboratory Manual for a complete list of TrialNet Core laboratories applicable to the TN19 protocol.	

For participating site contact information please refer to TN19 Contact Portlet located on the bottom of the protocol homepage of the member's website.



2. STUDY PERSONNEL RESPONSIBILITIES

2.1 Principal Investigator (Site PI)

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

1. Implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs) at the site to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements.
2. Ensure and confirm subject eligibility prior to randomization; reviewing inclusion/exclusion criteria with Study Chair or TNCC on a case-by-case basis, or as needed.
3. Ensure that all site investigators and research staff are appropriately qualified and fully aware of their obligations.
4. Ensuring local site initial and continuing Institutional Review Board (IRB)/Ethics Committee review and approval of the protocol (amendments, changes, updates, etc.).
5. Review local site adverse events (AEs) and ensure that AEs have been addressed appropriately and reported correctly.
6. Supervise the preparation of training materials and procedure manuals at the site.
7. Review all trial and patient care issues that occur at the local site.
8. Monitor protocol compliance at the local site and advise on appropriate response to protocol violations.

2.2 Trial Coordinator

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

1. Recruit potential participants.
2. Screen eligible participants.
3. Participate in enrollment.
4. Administer the consent process.
5. Coordinate participant visits.

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

2.3 Role of the TrialNet Coordinating Center

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

Specific responsibilities include:

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

3. STEPS TO SITE ACTIVATION AND ONGOING REGULATORY REQUIREMENTS

3.1 Requirements

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

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

1. Appropriate **IRB/ERB approval** (as below, section 3.2).
2. A current **Site Delegation Log (SDL)** detailing the responsibilities of each staff member as designated by the site PI (as below, section 3.3).
3. **Duality of Interest form(s)** for the PI and the main site coordinator (as below, section 3.4).
4. **Statement of Investigator, Form FDA 1572** (as below, section 3.5).
5. A completed **New Affiliate Application** consisting of the following forms:
 - a. Site Information Form (SIF)

- b. W9/W8 BEN (W8-BEN is used by non-US sites)
- c. New User forms for all site members listed on the Site Delegation Log
- d. Signed and Dated copy of PI's Curriculum Vitae (CV)
- e. TrialNet Confidentiality Agreement completed by all members listed on the SDL
- f. All persons listed on the SDL should complete an IRB/ERB approved human subjects education course

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

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

Requirements for IRB/ERB Approval:

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

3.3 Site Delegation Log

Requirements of the Site Delegation Log:

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

Background:

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

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

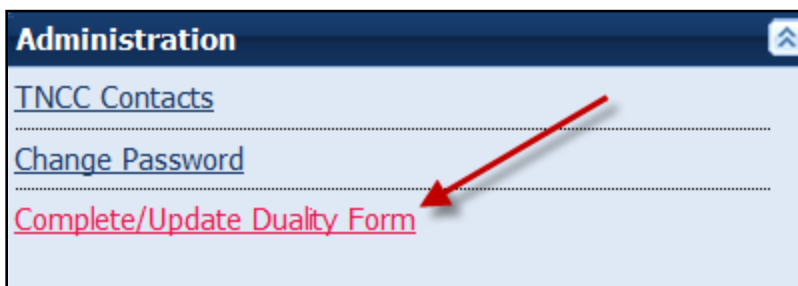
3.4 Duality of Interest Forms

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

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

To access the Duality of Interest form:

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



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

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

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

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

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

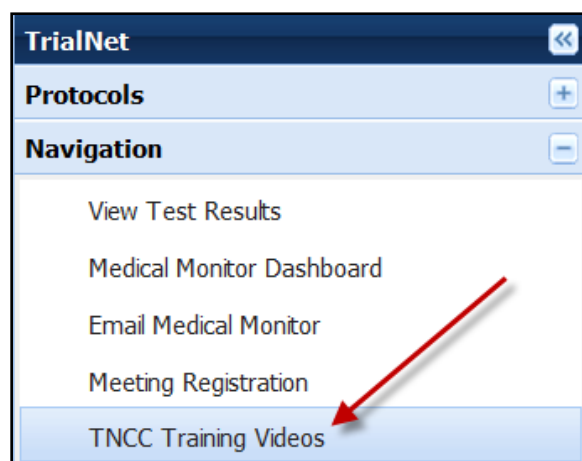
3.5 Study/System Training

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

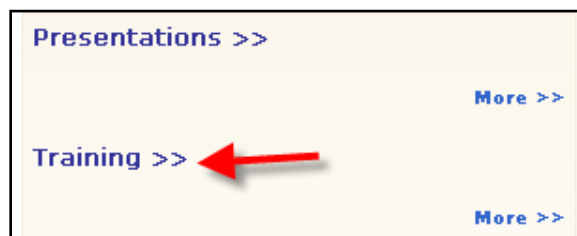
3.5.1 Online Training

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) TN19 Protocol Training Sessions Part 1 and Part 2: Provides a description of the protocol, eligibility criteria, purpose, specific aims, and details of procedures.
- 2) GENERAL Members Directory Overview: Provides a non-study specific overview of how to use the online member directory.
- 3) GENERAL Members Website Overview: Provides a non-study specific overview of how to use the online members' website.
- 4) 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 TN19 Certification Quiz is available online and can be completed by all individuals listed in roles on the Site Delegation Log requiring knowledge of study procedures. Once the certification quiz has been completed the site can request the answers from their clinical center to review.

3.6 Statement of Investigator, Form FDA 1572

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

3.6.1 Updating the 1572:

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

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

3.6.2 Who to include in Section 6:

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

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

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

3.7 Site Activation

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

3.8 Ongoing Regulatory Requirements

Once activated, a site must maintain current IRB/ERB approval. The study protocol must be reviewed at least annually by a site's IRB/ERB and documentation of an annual review must be submitted to the TNCC. This regulation applies to all TrialNet sites including international sites. (45CFR46.101 and 45CFR46.103(b)(4)).

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

3.8.1 Addition of New Site Staff

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

3.8.2 Removal of site staff

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

3.8.3 Site Contact Information Changes

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

3.8.4 New Primary Site Coordinator

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

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

3.8.5 Changes in Site PI

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

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

3.8.6 End Participation With TrialNet

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

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

4. RECRUITMENT PROCEDURES AND STRATEGIES

4.1 Recruitment Goals

84 Participants over 2 years

4.2 Recruitment Monitoring

Guidelines:

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

4.3 Eligibility Criteria

Inclusion Criteria:

The participant MUST:

1. Be 12 to 45 years of age at the time of randomization, this indicates that at the time of randomization the participant has passed his/her 12th birthday, but has not passed his/her 46th birthday
2. Be within 3-months (100 days) of diagnosis of Type 1 diabetes mellitus based on ADA criteria at the time of randomization.

The current ADA criteria for diagnosing diabetes include the following:

Fasting (no caloric intake for at least 8 hours) plasma glucose is ≥ 126 mg/dl (7.0 mmol/L)

Or

Diabetes symptoms (i.e. polyuria, polydipsia, polyphagia, and/or weight loss) exist and casual (any time of day without regard to time since last meal) plasma glucose is ≥ 200 mg/dl (11.1 mmol/L)

Or

2-hour plasma glucose is ≥ 200 mg/dl (11.1 mmol/L) during a 75 gram oral glucose tolerance test (OGTT)

Or

Unequivocal hyperglycemia with acute metabolic decompensation (e.g. ketoacidosis)

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

The date of diagnosis will be defined as follows:

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

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

3. Willing to provide Informed Consent or have a parent or legal guardian provide informed consent if the subject is <18 years of age
4. Must have at least one diabetes-related autoantibody present.
 - a. Islet-cell autoantibodies (ICA or IA-2H)
 - b. Glutamic acid decarboxylase autoantibodies (GAD65H) or
 - c. Micro-insulin autoantibody (mIAA)
 - i. If only MIAA positive, participant must have an additional autoantibody present if participant has been taking insulin therapy for longer than 10 days. If the initial screening antibody sample indicates that the participant is negative for all antibodies (or positive for mIAA only and participant has been taking insulin therapy for longer than 7 days), the participant is eligible for repeat testing as long as the repeat test is conducted within the eligibility windows (randomization must occur no more than 100-days from date of diagnosis and no more than 37 days from screening MMTT).
 - d. ZnT8
5. Have stimulated C-peptide levels ≥ 0.2 pmol/mL measured during a mixed meal tolerance test (MMTT) conducted at least 3 weeks (21 days) from diagnosis of diabetes and within one month (37 days) of randomization
6. Must be EBV PCR negative within two weeks of randomization if EBV seronegative at screening
7. Be at least 6 weeks from last live immunization
8. Must have received killed influenza vaccination at least 2 weeks prior to randomization when vaccine for the current or upcoming flu season is available
9. Be willing to forgo any vaccines (live or killed) for 3 months following last dose of study drug
10. Be willing to comply with intensive diabetes management

Exclusion Criteria:

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

1. Be immunodeficient or have clinically significant chronic lymphopenia: (Leukopenia (< 3,000 leukocytes / μ L), neutropenia (<1,500 neutrophils/ μ L), lymphopenia (<800 lymphocytes/ μ L), or thrombocytopenia (<100,000 platelets/ μ L).
2. Have active signs or symptoms of acute infection at the time of randomization
3. Have evidence of prior or current tuberculosis infection as assessed by PPD, interferon gamma release assay or by history
4. Be currently pregnant or lactating, or anticipate getting pregnant within the two year study period
5. Require use of other immunosuppressive agents including chronic use of systemic steroids
6. Have evidence of current or past HIV, Hepatitis B or Hepatitis C infection
7. Have any complicating medical issues or abnormal clinical laboratory results that may interfere with study conduct, or cause increased risk to include pre-existing cardiac disease, COPD, sickle cell disease, neurological, or blood count abnormalities
8. Have a history of malignancies other than skin
9. Evidence of liver dysfunction with AST or ALT greater than 3 times the upper limits of normal
10. Evidence of renal dysfunction with creatinine greater than 1.5 times the upper limit of normal
11. Vaccination with a live virus within the last 6 weeks of randomization
12. Current or ongoing use of non-insulin pharmaceuticals that affect glycemic control within prior 7 days of screening
13. Active participation in another T1D treatment study in the previous 30 days
14. Prior treatment with abatacept or anti-cd3
15. Known allergy to GCSF or ATG
16. Prior treatment with ATG or known allergy to rabbit derived products
17. Any condition that in the investigator's opinion may adversely affect study participation or may compromise the study results

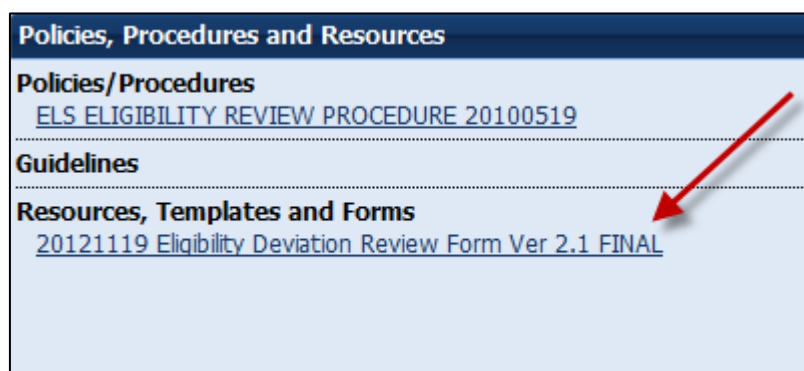
4.4 Exceptions to Questions Regarding Eligibility Criteria

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

4.4.1 Procedures for submission to the TrialNet Eligibility Committee

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

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



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

		Eligibility and Deviation Review Form Complete all highlighted sections		08Dec2009 Version 2.0 Page 1 of 1
Participant ID: 		Local Code: 		FTL:
Study: TN 		Study Name: 		
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>A. GENERAL INFORMATION</p> <p>1. Date of review request: (MM/DD/YYYY)</p> <p>2. Date response needed by: (MM/DD/YYYY)</p> </div> <div style="width: 50%; text-align: right; color: red;"> <p>Provide dates as indicated and complete this section.</p> </div> </div>				
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>B. GENERAL SUBJECT INFORMATION</p> <p>1. Age (years):</p> <p>2. Sex:</p> <p>3. Date of diagnosis with type 1 diabetes (if applicable): (MM/DD/YYYY)</p> <p>4. Date of screening visit (if applicable): (MM/DD/YYYY)</p> </div> <div style="width: 50%; text-align: right; color: red;"> <p>Complete this section & answer all questions</p> </div> </div>				
<p>C. ELIGIBILITY ISSUE DETAILS</p> <p>1. Provide a brief description of the eligibility issue/deviation that requires review:</p> <p style="color: red; font-weight: bold;">Note: In the description include dates if applicable i.e. visit timepoint & visit timepoint dates.</p> <p>2. Provide a brief justification for the subject's enrollment into the study:</p>				
<p>D. RELEVANT INFORMATION FROM STUDY DOCUMENTS</p> <p style="color: red; font-weight: bold;">If there is no relevant information, indicate "N/A".</p>				
TNCC USE ONLY				
<p>1. Eligibility reviewed? Y <input type="radio"/> N <input checked="" type="radio"/></p> <p style="color: red; font-weight: bold;">Sites should not complete this section only TNCC</p> <p>IF YES,</p> <p>a. Date of review: </p> <p>b. Reviewer: TNCC Committee Chair Full Committee</p> <p>c. Eligibility decision: Eligible Not Eligible</p> <p>IF NO,</p> <p>a. Reason not reviewed: </p> <p>2. Comments: </p>				

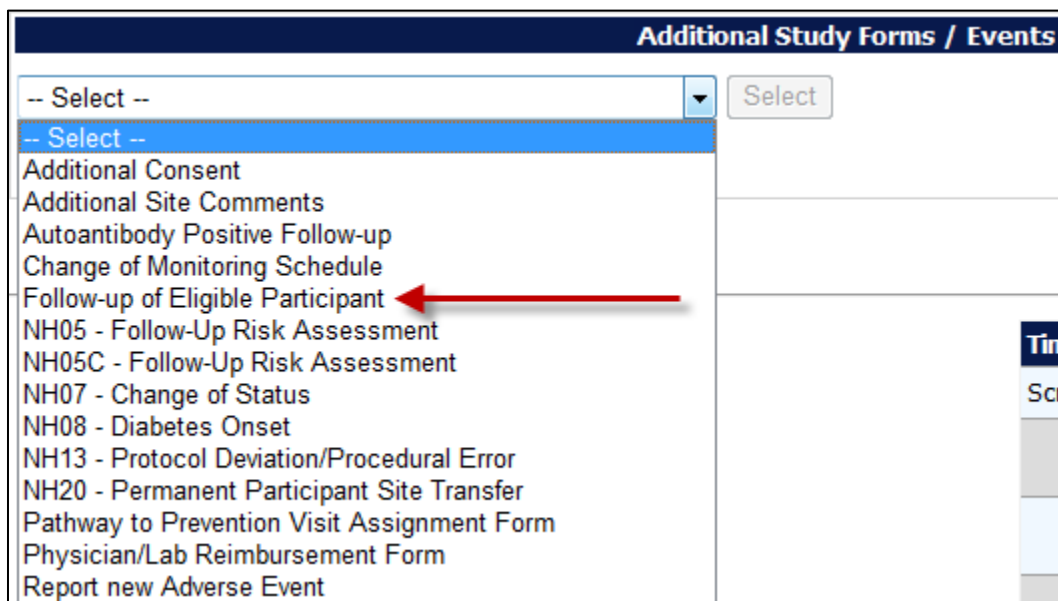
4.5 Follow-up of Eligible Study Participant

For Current TrialNet Participants:

Once a participant has been asked to participate in this study the site can 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 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, then a new form should be completed.

For Participants Outside of TrialNet:

Please notify the TN19 CRA for follow up of eligible participant that did not originate from a TrialNet study.

5. VISIT PROCEDURES

The source documents for all visits are located on the members website in the TN19 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 TN19 laboratory Manual of Operations.

5.1 Visit -1 Screening

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Order any supplies needed for the study procedures through the online Fisher BioServices Supply Ordering System.	NA	NA
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc.). Refer to instructions above for location of visit checklists.	NA	NA
Pre-visit	Remind the participant that they need to be fasting for this visit.	NA	NA
Pre-visit	Assess flu vaccination status and order vaccine from EMINENT if applicable* <i>*We prefer that the participant obtain the flu vaccine at the screening visit in order to measure the immunological response to the vaccine.</i>	NA	NA
At Visit	Administer the screening consent and if applicable screening assent, local HIV screening consent, and local HIPAA form.	Consent & Assent	Screening Informed Consent Verification
At Visit	Register the participant in the online system Please Note: If the participant enrolled from another TrialNet Study, then the PID registered should be the same PID in their originating study.	NA	Participant Registration
At Visit	Administer the volunteer understanding assessment. Coordinator should review the assessment with the participant and parents (if applicable) taking special care to review any incorrect answers. Coordinator should also document assessment review.	Volunteer Understanding Assessment	NA
At Visit	Collect participant’s medical history	Complete Medical History	Screening Medical History

At Visit	Ask the participant about what medications he/she is currently taking. Please enter one medication per line. eCRF should be saved after each entry is added.	ConMeds	Concomitant Medication
At Visit	Conduct a physical exam	Complete PE	Physical Exam
At Visit	Administer flu vaccine	Flu Vaccination	Flu Vaccination
At Visit	Conduct an IGRA test	Local IGRA Source	NA
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Screening Visit Assessment
At Visit	Conduct a Urinalysis. For guidance on completing the UA, please refer to Appendix C	UA Assessment	Urinalysis Evaluation
At Visit	Conduct a 4-hour MMTT For guidance on collecting the MMTT, please refer to Appendix D.	Local MMTT Source	Screening Specimen Collection
At Visit	Local Lab Collections: 1. Whole Blood – CBC with differential	Lab Results signed and dated by MD or delegated personnel	CBC with differential Results
At Visit	Central Lab Collections: 1. Serum – Chemistries 2. Serum – HIV/Hep B/Hep C Serology 3. Serum – Autoantibodies 4. HbA1c 5. Serum – EBV/CMV Viral Serology 6. Whole Blood-EBV PCR	Signed and dated printout of specimen collection form	Screening Specimen Collection
At Visit	Remind participant to bring blood glucose and insulin records to next visit.	Participant Log	NA
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit**	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms. Please Note: Please send all Screening Specimens as priority by checking "priority" for each sample in the online specimen collection form. Please review the Laboratory Manual of Operations and Specimen System User Manual for additional information about priority samples	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS.	NA	NA

	Refer to the SMS Manual for detailed instructions 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

* For specific instructions on how to conduct an MMTT please see appendix A. (For the location of all appendices please reference section 15)

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

5.1.1 Screen Failures

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

- Step 1. Enter all data collected for the screening visit into the eCRF.
- Step 2. Complete the Screening Eligibility form. Once this form is saved, the participant's status will be marked as "Not Eligible".
- Step 3. Complete the PRN "Change of Status" Form:
 - a. Select Status Change Information as "An active participant withdraws"
 - b. Select Participant Withdrawing from the Study as "Ineligible to Randomize"
 - c. Indicate whether or not the participant is still willing to be contacted.
- Step 4. Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.

5.1.2 Rescreen Procedures

Rescreen within 30 days:

A participant who is eligible for rescreening may need to wait at least 2 weeks following the initial screening visit prior to the rescreen visit. If they are eligible for rescreening within 30 days of the initial screening visit, the following procedures are required:

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Site should review subject's CBC, Chemistries, and infectious disease serologies from the subject's initial screening visit. Specimen collections that were abnormal at screening will need to be repeated at the rescreen.	NA	NA
At Visit	Collect participant's family and medical history.	Complete Medical History	Screening Visit Assessment
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	ConMeds	Concomitant Medications

	added.		
At Visit	Conduct a physical exam.	Complete PE	Screening Visit Assessment
At Visit	Conduct a Urine Pregnancy Test (if applicable).	Pregnancy Monitoring	Screening Visit Assessment
At Visit	Conduct a Urinalysis.	UA Assessment	Urinalysis Evaluation
At Visit	<u>The following collections are only required if abnormal at initial screening visit:</u> Local Lab Collections: <ol style="list-style-type: none"> Whole Blood – CBC with differential 	Lab Results signed and dated by MD or delegated personnel	CBC with differential Results
At Visit	<u>The following collections are only required if abnormal at initial screening visit:</u> Central Lab Collections: <ol style="list-style-type: none"> Serum – Chemistries Serum – HIV/Hep B/Hep C Serology Serum – Autoantibodies HbA1c Serum – EBV/CMV Viral Serology Whole Blood-EBV PCR 	Signed and dated printout of specimen collection form	Screening Specimen Collection
At Visit	Conduct a 4 hour MMTT (if applicable). Please Note: Please contact the TN19 CRA to confirm if an additional MMTT is required to be collected at the rescreening visit	Local MMTT Source and Signed Specimen Collection Form	Screening Specimen Collection
Post Visit	Complete the “Change of Status” PRN form in the online system to reactivate participant.	NA	Change of Status (PRN)
Post Visit	Enter data collected on source documents into the e-CRFs online.	NA	NA
Post Visit*	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the Specimen Management System (SMS) Manual for detailed instructions on the completion of collection forms. Please Note: Please send all Screening Specimens as priority by checking “priority” for each sample in the online specimen collection	NA	NA

	form. Please review the Laboratory Manual of Operations and Specimen System User Manual for additional information about priority samples.		
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.

Rescreen after 30 days:

A participant who is eligible for rescreening should wait at least 2 weeks following the initial screening visit prior to the rescreen visit. If participant becomes eligible to rescreen outside of 30 days a full screening visit is required

5.2 Visit 0^A Infusion (Baseline, Day 0):

Window: Within 37 days of screening MMTT and 100 days from diagnosis

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. Please print out a copy of the participant's eligibility labs. PI needs to sign as source document. Please Note: Randomization <u>MUST</u> occur <= 100 days from T1DM diagnosis.	Signed and dated print out of eligibility labs	N/A
Pre-visit	Schedule the participant for a baseline visit. Remind subject to bring glucometer to visit.		
Pre-visit	Complete the online Baseline Eligibility eCRF Please Note: Upon completion of the form, the status of the participant should indicate "eligible". If the participant's status reflects eligible, proceed to randomizing the participant. If not, please contact the TNCC.	Eligibility Form	Baseline Eligibility

Pre-visit	<p>For the first participant: Contact the TNCC no less than 1-week prior to the baseline visit date and notify the TNCC that a participant is scheduled for a baseline visit and that initial study drug is needed.</p> <p>For all subsequent participants: follow procedures outlined in the Pharmacy Manual for the ordering of study drug.</p>	Agent Request Form	N/A
Pre-visit	Order any supplies needed for the study procedures through the online Fisher BioServices Supply Ordering System (SOS).	N/A	N/A
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, etc.).	NA	NA
At Visit	<p>Randomize participant online. Within the protocol homepage, select "Assign Treatment". Please refer to section 9.3.11 for additional instructions on randomizing a participant.</p> <p>Please Note: Print the randomization number form and place in the source documents.</p>	N/A	Assign Treatment
At Visit	Administer the intervention consent (and assent if participant is under the age of 18), (if not completed at screening visit).	Consent	NA
At Visit	Administer the volunteer survey (if not done at screening visit). Coordinator should review the survey with the participant and parents (if applicable) taking special care to review any incorrect answers.	Volunteer Understanding Assessment	NA
At Visit	Collect participant's interim medical history	Interim Medical History	Interim Medical History
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Conduct a physical exam	Interim PE	Interim Physical Exam
At Visit	Obtain information about Diabetes Management	Diabetes Management	Diabetes Management
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Conduct a Urinalysis	UA Assessment	Urinalysis Evaluation
At Visit	<p>Baseline lab collection:</p> <ol style="list-style-type: none"> 1. CD4/CD8 Ratio 2. Chemistries/LFT 3. IgG 	Signed and dated printout of specimen collection form	Screening Specimen Collection

	4. Whole Blood – PBMC/Plasma 5. Whole Blood – RNA 6. Serum – Mechanistic Serum		
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s). Refer to the SMS Manual for detailed instructions on the completion of collection forms.	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

5.3 Visit 0^B Infusion (Baseline, Day 1):

Window: Next Day

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, etc.).	NA	NA
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher)	AE assessment	Adverse Events
At Visit	Administer study agent	Study Drug Administration	Study Drug Administration
At Visit	Visit lab collection*: 1. CBC with differential 2. Serum – Mechanistic Serum <i>*Please note- this collection should occur approximately 5 minutes post infusion #1</i>	Signed and dated printout of specimen collection form	Screening Specimen Collection
At Visit	Remind participant to bring blood glucose and insulin records to next visit.	NA	NA
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s).	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions	NA	NA

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

5.4 Visit 0^c Infusion (Baseline, Day 2):

Window: + 1 Day from Visit 0^B Baseline

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, etc.).	NA	NA
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher)	AE assessment	Adverse Events
At Visit	Administer study agents (ATG Infusion/Placebo Infusion plus GCSF Injection/Placebo Injection)	Study Drug Administration	Study Drug Administration
At Visit	Visit lab collection*: 1. Serum – Mechanistic Serum <i>*Please note- this collection should occur approximately 5 minutes post infusion #2</i>	Signed and dated printout of specimen collection form	Screening Specimen Collection
At Visit	Remind participant to bring blood glucose and insulin records to next visit.	NA	NA
At Visit	Provide the participant with the study prescription sheet for all outpatient side effect medications, including prednisone*. This information is to be given to participants at discharge with instructions not to fill, unless needed. <i>(please see Appendix J for details on medication list.)</i> *participants should be instructed to contact the Study PI and the Central Review Team before taking prednisone. <i>(please refer to Appendix J for contact details)</i>		
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit	Scan barcodes for each central laboratory sample into the online specimen collection form(s).	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post	Retain all materials from visit, and source	NA	NA

Visit	documents in an organized fashion in a secured, double-locked room.		
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5.5 Visit 1 (Week 2):

Window: 14 days after Infusion (Baseline 0^B)(+/- 3 days)

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Schedule the participant for the visit.	NA	NA
Pre-visit	Remind the participant to bring glucometer for the visit and diabetes management/insulin log.	NA	NA
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc).	NA	NA
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Conduct a physical exam and vital signs.	PE	PE Visit Assessment
At Visit	Obtain information about Diabetes Management	Diabetes Management	Diabetes Management
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Conduct a Urinalysis.	UA Assessment	Urinalysis Evaluation
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher). If Grade 1, PI needs to sign source document.	AE assessment	Adverse Events
At Visit	Download the subject's meter or pump. Ask the participant about insulin use and hypoglycemic events.	Disease Specific Assessment and Participant Insulin use logs	Diabetes Management Form
At Visit	Local lab collection: 1. CBC with Differential	Lab Results signed and dated by MD or delegated personnel	CBC with differential Results
At Visit	Central lab collection: 1. Chemistries/LFT 2. Mechanistic Assessments	Signed and dated specimen collection form	Week 2 Specimen Collection

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

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

5.6 Visit 2 (Week 4):

Window: 28 days after Baseline (+/- 3 days)

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Schedule the participant for the visit.	NA	NA
Pre-visit	Remind the participant to bring glucometer for the visit.	NA	NA
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc).	NA	NA
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Conduct a physical exam and vital signs.	PE	PE Visit Assessment
At Visit	Obtain information about Diabetes Management	Diabetes Management	Diabetes Management
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Conduct a Urinalysis.	UA Assessment	Urinalysis Evaluation
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher). If Grade 1, PI needs to sign	AE assessment	Adverse Events

	source document.		
At Visit	Download the subject's meter or pump. Ask the participant about insulin use and hypoglycemic events.	Disease Specific Assessment and Participant Insulin use logs	Diabetes Management Form
At Visit	Local lab collection: 1. CBC with Differential	Lab Results signed and dated by MD or delegated personnel	CBC with differential Results
At Visit	Central lab collection: 1. Chemistries/LFT 2. Mechanistic Assessments 3. CD4/CD8 Ratio	Signed and dated specimen collection form	Week 2 Specimen Collection
At Visit	Administer Study Agent (GCSF injection/Placebo)	Study Drug Administration	Study Drug Administration
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit*	Scan barcodes for each central laboratory sample into the online specimen collection form(s).	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

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

5.7 Visit 3 (Week 6):

Window: 42 days after Baseline (+/- 3 days)

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Schedule the participant for the visit.	NA	NA
Pre-visit	Remind the participant to bring glucometer for the visit.	NA	NA
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc).	NA	NA
At Visit	Ask the participant about any changes in	Concomitant	Concomitant

	medication since last visit	Medications	Medications
At Visit	Conduct a physical exam and vital signs.	PE	PE Visit Assessment
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Conduct a Urinalysis.	UA Assessment	Urinalysis Evaluation
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher). If Grade 1, PI needs to sign source document.	AE assessment	Adverse Events
At Visit	Local lab collection: 1. CBC with Differential	Lab Results signed and dated by MD or delegated personnel	CBC with differential Results
At Visit	Central lab collection: 1. Chemistries/LFT	Signed and dated specimen collection form	Week 2 Specimen Collection
At Visit	Administer Study Agent (GCSF injection/Placebo)	Study Drug Administration	Study Drug Administration
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit*	Scan barcodes for each central laboratory sample into the online specimen collection form(s).	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

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

5.8 Visit 4 (Week 8):

Window: 56 days after Baseline (+/- 3 days)

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Schedule the participant for the visit.	NA	NA
Pre-visit	Review visit checklist and ensure site is prepared	NA	NA

	for visit (procedures, supplies, etc).		
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Conduct a physical exam and vital signs.	PE	PE Visit Assessment
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Conduct a Urinalysis.	UA Assessment	Urinalysis Evaluation
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher). If Grade 1, PI needs to sign source document.	AE assessment	Adverse Events
At Visit	Local lab collection: 1. CBC with Differential	Lab Results signed and dated by MD or delegated personnel	CBC with differential Results
At Visit	Central lab collection: 1. Chemistries/LFT 2. Mechanistic Assessments 3. CD4/CD8 Ratio	Signed and dated specimen collection form	Week 2 Specimen Collection
At Visit	Administer Study Agent	Study Drug Administration	Study Drug Administration
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit*	Scan barcodes for each central laboratory sample into the online specimen collection form(s).	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

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

5.9 Visit 5 (Week 10):

Window: 70 days after Baseline (+/- 3 days)

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Schedule the participant for the visit.	NA	NA
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc).	NA	NA
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Conduct a physical exam and vital signs.	PE	PE Visit Assessment
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher). If Grade 1, PI needs to sign source document.	AE assessment	Adverse Events
At Visit	Download the subject's meter or pump. Ask the participant about insulin use and hypoglycemic events.	Disease Specific Assessment and Participant Insulin use logs	Diabetes Management Form
At Visit	Local lab collection: 1. CBC with Differential	Lab Results signed and dated by MD or delegated personnel	CBC with differential Results
At Visit	Central lab collection: 1. Chemistries/LFT 2. Mechanistic Assessments	Signed and dated specimen collection form	Week 2 Specimen Collection
At Visit	Administer Study Agent	Study Drug Administration	Study Drug Administration
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit*	Scan barcodes for each central laboratory sample into the online specimen collection form(s).	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured,	NA	NA

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

5.10 Visit 6 (Week 12):

Window: 84 days after Baseline (+/- 3 days)

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Schedule the participant for the visit.	NA	NA
Pre-visit	Remind the participant to bring glucometer for the visit and remind participant to fast before next visit	NA	NA
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc).	NA	NA
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Conduct a physical exam and vital signs.	PE	PE Visit Assessment
At Visit	Obtain information about Diabetes Management	Diabetes Management	Diabetes Management
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher). If Grade 1, PI needs to sign source document.	AE assessment	Adverse Events
At Visit	Download the subject's meter or pump. Ask the participant about insulin use and hypoglycemic events.	Disease Specific Assessment and Participant Insulin use logs	Diabetes Management Form
At Visit	Local lab collection: 1. CBC with Differential	Lab Results signed and dated by MD or delegated personnel	CBC with differential Results

At Visit	Central lab collection: 1. Chemistries/LFT 2. Mechanistic Assessments 3. HbA1c 4. CD4/CD8 Ratio	Signed and dated specimen collection form	Week 2 Specimen Collection
At Visit	Conduct a 2 hour MMTT. For guidance on collecting the MMTT, please refer to Appendix D.	Local MMTT Source and Signed Specimen Collection Form	Screening Specimen Collection
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit*	Scan barcodes for each central laboratory sample into the online specimen collection form(s).	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

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

5.11 Visit 7 (Week 24):

Window: 174 days after Baseline (+/- 7 days)

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Schedule the participant for the visit.	NA	NA
Pre-visit	Remind the participant to bring glucometer for the visit.	NA	NA
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc).	NA	NA
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Conduct a physical exam and vital signs.	PE	PE Visit Assessment
At Visit	Obtain information about Diabetes Management	Diabetes Management	Diabetes Management

At Visit	Ask the participant to complete the initial study Participant Survey*	Participant Survey	NA
	<i>* This survey is to be completed at 6 months, 12 months and (final survey) at 2 years in this study.</i>		
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher). If Grade 1, PI needs to sign source document.	AE assessment	Adverse Events
At Visit	Download the subject's meter or pump. Ask the participant about insulin use and hypoglycemic events.	Disease Specific Assessment and Participant Insulin use logs	Diabetes Management Form
At Visit	Local lab collection: 1. CBC with Differential	Lab Results signed and dated by MD or delegated personnel	CBC with differential Results
At Visit	Central lab collection: 1. Chemistries/LFT 2. Mechanistic Assessments 3. HbA1c 4. CD4/CD8 Ratio	Signed and dated specimen collection form	Week 2 Specimen Collection
At Visit	Conduct a 2 hour MMTT. For guidance on collecting the MMTT, please refer to Appendix D.	Local MMTT Source and Signed Specimen Collection Form	Screening Specimen Collection
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit*	Scan barcodes for each central laboratory sample into the online specimen collection form(s).	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

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

5.12 Visit 8 (Week 36):

Window: 264 days after Baseline (+/- 7 days)

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Schedule the participant for the visit.	NA	NA
Pre-visit	Remind the participant to bring glucometer for the visit.	NA	NA
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc).	NA	NA
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Conduct a physical exam and vital signs.	PE	PE Visit Assessment
At Visit	Obtain information about Diabetes Management	Diabetes Management	Diabetes Management
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher). If Grade 1, PI needs to sign source document.	AE assessment	Adverse Events
At Visit	Download the subject's meter or pump. Ask the participant about insulin use and hypoglycemic events.	Disease Specific Assessment and Participant Insulin use logs	Diabetes Management Form
At Visit	Local lab collection: 1. CBC with Differential	Lab Results signed and dated by MD or delegated personnel	CBC with differential Results
At Visit	Central lab collection: 1. Chemistries/LFT 2. Mechanistic Assessments 3. HbA1c 4. CD4/CD8 Ratio	Signed and dated specimen collection form	Week 2 Specimen Collection
At Visit	Conduct a 2 hour MMTT. For guidance on collecting the MMTT, please refer to Appendix D.	Local MMTT Source and Signed Specimen Collection Form	Screening Specimen Collection
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA

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

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

5.13 Visit 9 (Week 48):

Window: 354 days after Baseline (+/- 7 days)

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Schedule the participant for the visit.	NA	NA
Pre-visit	Remind the participant to bring glucometer for the visit.	NA	NA
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc).	NA	NA
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Conduct a physical exam and vital signs.	PE	PE Visit Assessment
At Visit	Obtain information about Diabetes Management	Diabetes Management	Diabetes Management
At Visit	Ask the participant to complete the initial study Participant Survey* * This survey is to be completed at 6 months, 12 months and (final survey) at 2 years in this study.	Participant Survey	NA
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher). If Grade 1, PI needs to sign source document.	AE assessment	Adverse Events

At Visit	Download the subject's meter or pump. Ask the participant about insulin use and hypoglycemic events.	Disease Specific Assessment and Participant Insulin use logs	Diabetes Management Form
At Visit	Local lab collection: 1. CBC with Differential	Lab Results signed and dated by MD or delegated personnel	CBC with differential Results
At Visit	Central lab collection: 1. Chemistries/LFT 2. Mechanistic Assessments 3. HbA1c 4. CD4/CD8 Ratio 5. Serum – EBV/CMV Viral Serology 6. Whole Blood-EBV PCR	Signed and dated specimen collection form	Week 2 Specimen Collection
At Visit	Conduct a 4 hour MMTT. For guidance on collecting the MMTT, please refer to Appendix D.	Local MMTT Source and Signed Specimen Collection Form	Screening Specimen Collection
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit*	Scan barcodes for each central laboratory sample into the online specimen collection form(s).	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

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

5.14 Visit 10 (Week 72):

Window: 534 days after Baseline (+/- 14 days)

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Schedule the participant for the visit.	NA	NA
Pre-visit	Remind the participant to bring glucometer for the	NA	NA

	visit.		
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc).	NA	NA
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Conduct a physical exam and vital signs.	PE	PE Visit Assessment
At Visit	Obtain information about Diabetes Management	Diabetes Management	Diabetes Management
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher). If Grade 1, PI needs to sign source document.	AE assessment	Adverse Events
At Visit	Download the subject's meter or pump. Ask the participant about insulin use and hypoglycemic events.	Disease Specific Assessment and Participant Insulin use logs	Diabetes Management Form
At Visit	Local lab collection: 1. CBC with Differential	Lab Results signed and dated by MD or delegated personnel	CBC with differential Results
At Visit	Central lab collection: 1. Chemistries/LFT 2. Mechanistic Assessments 3. HbA1c	Signed and dated specimen collection form	Week 2 Specimen Collection
At Visit	Conduct a 4 hour MMTT. For guidance on collecting the MMTT, please refer to Appendix D.	Local MMTT Source and Signed Specimen Collection Form	Screening Specimen Collection
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit*	Scan barcodes for each central laboratory sample into the online specimen collection form(s).	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
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*Depending upon site workflow, barcodes may be scanned prior to, during, or after the visit.

5.15 Visit 11 (Week 96):

Window: 714 days after Baseline (+/- 14 days)

Time Point	Description of Procedure	Source Document	eCRFs
Pre-visit	Schedule the participant for the visit.	NA	NA
Pre-visit	Remind the participant to bring glucometer for the visit.	NA	NA
Pre-visit	Review visit checklist and ensure site is prepared for visit (procedures, supplies, etc).	NA	NA
At Visit	Ask the participant about any changes in medication since last visit	Concomitant Medications	Concomitant Medications
At Visit	Conduct a physical exam and vital signs.	PE	PE Visit Assessment
At Visit	Obtain information about Diabetes Management	Diabetes Management	Diabetes Management
At Visit	Conduct a Urine Pregnancy Test (if applicable)	Pregnancy Monitoring	Pregnancy Monitoring
At Visit	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher). If Grade 1, PI needs to sign source document.	AE assessment	Adverse Events
At Visit	Download the subject's meter or pump. Ask the participant about insulin use and hypoglycemic events.	Disease Specific Assessment and Participant Insulin use logs	Diabetes Management Form
At Visit	Local lab collection: 1. CBC with Differential	Lab Results signed and dated by MD or delegated personnel	CBC with differential Results

At Visit	Central lab collection: 1. Chemistries/LFT 2. Mechanistic Assessments 3. HbA1c	Signed and dated specimen collection form	Week 2 Specimen Collection
At Visit	Conduct a 4 hour MMTT. For guidance on collecting the MMTT, please refer to Appendix D.	Local MMTT Source and Signed Specimen Collection Form	Screening Specimen Collection
Post Visit	Enter data collected on source documents into the e-CRF's online.	NA	NA
Post Visit*	Scan barcodes for each central laboratory sample into the online specimen collection form(s).	NA	NA
Post Visit	Ship specimens to lab(s) using the online SMS. Refer to the SMS Manual for detailed instructions on use of the electronic shipping system.	NA	NA
Post Visit	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

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

5.16 Interim Contacts

*Window: Every week between visits**

Time Point	Description of Procedure	Source Document	eCRFs
During Call	Collect participant's interim medical history (changes since last visit).	Document Correspondence	NA
At Visit	Ask the participant about hypoglycemic events.	Document Correspondence	NA
During Call	Ask the participant about any changes in medication since last visit.	Concomitant Medications	Concomitant Medications
During Call	Ask the participant if they have experienced any adverse events (eCRF to be completed only if Grade 2 or higher).	AE assessment	Adverse Events
Post Call	Retain all materials from visit, and source documents in an organized fashion in a secured, double-locked room.	NA	NA

* Contact with participant will occur daily following ATG infusions for 2 weeks, and weekly thereafter.

5.17 PRN/Unscheduled Study Visits

If the participant is requested to come in for an unscheduled visit not reviewed in the schedule of assessments (experiencing an SAE, etc), please contact the Protocol Chair, the Medical Monitor, and the TNCC for additional instructions.

5.18 Description of Study Procedures

5.18.1 Randomization/Treatment Assignment (Baseline)

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

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

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

- ATG
- ATG + GCSF
- Placebo

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

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

Please refer to Section 9.3.9 for additional instructions on how to randomize a participant.

5.18.2 Study Drug Administration (Visits 0^B-0^C, and Visits 1-5)

ATG: (Visits 0^B-0^C)

Two treatment infusions of ATG or placebo will be given at the research site over a period of 2-3 days and one treatment injection of GCSF or placebo after completing the second infusion. (If assigned to receive ATG, a total of 2.5 mg/each kg of body weight is given)

The study treatment infusion of ATG or placebo is given by placing a needle and/or plastic tube (IV) in participant's arm. This IV will be left in place for the duration of the visit which will take 2-3 days. Participant will be given two infusions of ATG or placebo. The first study treatment infusion will be given continuously and will take between 12 to 20 hours. There will be 12-24 hour break between infusions. The second infusion will take from 8 to 16 hours. The length of the visit and the time for each infusion depends on whether the participant has reactions or side effects from the study treatment. The maximum allowable timeframe from start of infusion to completion is 60 hours.

At least 30 minutes before each infusion participant will receive acetaminophen, an antihistamine to prevent or decrease the immediate reactions to the study treatment as well as another medication called methylprednisolone or placebo which is used to suppress inflammation. Additional acetaminophen or antihistamine will be given as need to treat any reactions to the study medication. The study participant will also receive methylprednisolone or placebo 12 hours after the start of each infusion

Beginning at the time the infusion starts the following will be checked: measured temperature, blood pressure and pulse every 30 minutes for the first two hours and then every hour until the infusion is completed

GCSF: (Visits 0^c and Visits 1-5)

Approximately 6 hours after completing the study treatment infusion, begin the first of 6 study treatment injections. The injection is given subcutaneously. The participant will return to the study site for 5 additional injections to be given every two weeks, over the following ten weeks.

All injection site or related adverse events should be treated as needed (warmth, redness, pain, swelling, itching) and documented in the source.

5.18.3 AE (Adverse Event) Assessment (All Visits)

Definitions:

Adverse event in this clinical trial is defined as *"any occurrence or worsening of an undesirable or unintended sign, symptom or disease whether or not associated with the treatment and study procedures."*

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

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

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

Important medical events that may not result in death, be life threatening, or require

hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Reportable Adverse Event: defined per protocol. This study has adopted usage of the National Cancer Institute (NCI) Common Technology Criteria for Adverse Events (CTCAE) version 4.0 and/or study-specific criteria for classification to describe the severity of adverse events with the exception of hyper and hypoglycemia. For this study, a reportable hypoglycemic event is defined as those resulting in loss of consciousness, seizure, or requiring assistance of others due to altered state of consciousness and hyperglycemic event is one resulting in DKA. Only AE's determined to be CTCAE 4.0 grade 2 or greater are reportable and should be submitted to the GCC using the online AE reporting system. ALL serious adverse events (regardless of grade or relatedness to disease progression) must be reported.

Reporting Timeline:

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

Procedure:

- Step 1. Utilize source document as a guide.
- Step 2. Ask participant if they have experienced any new or worsening symptoms since last visit. If yes, proceed to step 3.
- Step 3. Complete AE report in online system (if applicable).
- Step 4. Fulfill any local site reporting requirements (to ethics board/IRB/etc).
- Step 5. If AE is a serious adverse event which the medical monitor and/or investigator** judge as unexpected and possibly, probably or definitely related to study agent, the coordinator should complete FORM FDA3500A (MedWatch Report), submit to the FDA, and immediately fax/email to the TNCC.

***All events that are serious, unexpected, and possibly, probably, or definitely related to study drug based on Medical Monitor review require submission of a MedWatch report to the Coordinating Center *within 24 hours of when the site was notified of the event* (even if the Medical Monitor's review differs from the investigator's assessment). Regardless, in the event that the investigator feels compelled to submit a MedWatch report (even if, per the Medical Monitor's review, a MedWatch is not required) the investigator is free to do so.

Please refer to the following website for additional information and a printable version of the NCI-CTCAE manual:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

5.18.4 Clinical Assessments

5.18.2.1 Screening and Interim Medical History

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

Procedure:

- Step 1. Utilize source document as a guide.
- Step 2. Complete all sections of the source document (answer all questions).
- Step 3. Enter data from source document into the online eCRF (all applicable fields).

5.18.5 Complete Physical Exam (Screening, Baseline, Visit 2, Visit 3, Visit 4, Visit 7, Visit 9, Visit 10, and Visit 11)

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

Procedure:

- Step 1. Utilize source document as a guide.
- Step 2. Collect the following physical assessments:
 - a. Weight: Record the participant's weight as kilograms. Shoes should routinely be removed when taking this assessment.
 - b. Height: Record the participant's height as centimeters. Shoes should routinely be removed when taking this assessment. Participants less than 18 years of age should have their height assessed using a stadiometer, if available.
 - i. Height should be recorded for all participants at the Screening Visit
 - ii. Height should only be measured for subjects <18 years of age after the Screening Visit
 - c. Seated arm blood pressure: Record the systolic and diastolic arm pressure while the participant is seated.
 - d. Temperature: Record the participant's temperature as degrees Celsius.
 - e. Heart rate
 - f. Respiratory rate
 - g. Review Systems: Record whether systems are reported as normal or abnormal by the participant and normal or abnormal upon examination. If either the participant or the clinical indicated an abnormality for any of the systems, explain the abnormality.
 - i. For "Other", please note any other abnormal clinical findings from the physical exam.

- ii. Genitalia is required to be assessed only if the participant reports as abnormal.
 - h. Tanner Stage:
 - i. For the Baseline Visit, indicate the participant's sexual development using the Tanner Scale and record whether the participant is in Stage 1, Stage 2, or Stage 3 breast (female), genitalia (male) and pubic hair (both). Note that Tanner Staging is completed for participants once Tanner Stage 3 is reached.
 - ii. Tanner Stage should only be re-assessed at Visit 9 (Week 48) and Visit 11 (Week 96) AND if Tanner Stage < 3 at previous visits.
 - iii. See Appendix H for the Tanner Stage descriptions.
- Step 3. Complete all sections of the source document (answer all questions).
- Step 4. Enter data from source document into the online eCRF (all applicable fields).

5.18.6 Pregnancy Monitoring (Visits Screening, Baseline 0^A and Visits 1-11)

- Step 1. Females:
- Urine pregnancy tests are required for all females with childbearing potential. The test results and method of birth control (including abstinence) should be noted on the source document.
- Step 2. Males:
- Method of birth control used with their partners should be noted on the source document. If participant is not sexually active abstinence should be noted for birth control method. The use of effective birth control for up to 6 months following randomization may be considered in men who are sexually active but is not required for study participation.

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 MMTT if the participant is confirmed pregnant).
- Step 3. Ask the participant if they would be willing to be followed on the study to record information about their pregnancy outcome.
- a. If the participant does not want to be followed, withdraws consent, or becomes lost to follow up complete the "Change in Status" form. If the participant agrees to be followed,
 - i. At the end of the pregnancy, document the pregnancy outcome on the "Pregnancy Outcome" PRN e-CRF.
 - ii. Complete study visits as per the study schedule but **DO NOT** administer any further doses of study drug and **DO NOT** conduct any further MMTT's.
- Step 4. Place a note to file in the participant binder documenting the conversation and the outcome (i.e. participant agrees to be followed per study, participant does not agree to be followed per study, etc.).

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

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

5.18.7 Concomitant Medications (All Visits)

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

Please Note: Insulin use is captured on the Diabetes Management Case Report Form and should not be included on the Conmed eCRF.

Procedure:

Step 1. Utilize source document as a guide.

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

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

Please Note: For additional information, please refer to the Concomitant Medications training document posted in Appendix I.

5.18.8 CBC with Differential Assessment (Visits: Screening (-1), Baseline (0^B), and Visit 1-11)

Definition: A complete blood count with differential (a.k.a CBC with differential) measures the levels of red blood cells, white blood cells, platelet levels, hemoglobin and hematocrit. Many times it is ordered as a screening test, as an anemia check or as a test for infection. The CBC with differential can be used to aid in diagnosing and treating a large number of other conditions. This test is run locally.

Please consult with your local lab/institution for collection and processing procedures.

5.18.9 Interferon-Gamma Release Assays (IGRA)

Definition: Interferon-Gamma Release Assays (IGRAs) are whole-blood tests that can aid in diagnosing Mycobacterium tuberculosis infection. This test is run locally.

Please consult with your local lab/institution for collection and processing procedures.

5.18.10 *Urinalysis Evaluation (Screening, Baseline (0^A), Visit 1, Visit 2, Visit 3 and Visit 4)*

Definition: A urinalysis (UA) is an examination of the urine to determine the general health of the body and, specifically, kidney function, usually including measurement of pH, tests for protein, glucose, ketones, and blood.

Procedure:

- Step 1. Utilize source document as a guide.
- Step 2. Perform UA (Please refer to Appendix C. for additional instructions for completing the UA).
- Step 3. Enter data from source document into the online eCRF (all applicable fields).

5.18.11 *Intensive Diabetes Management*

During the study, all participants will receive “intensive” management of their diabetes, and HbA1C will be assessed every 3 months to evaluate metabolic control. The goal of treatment will be to maintain the HbA1C level as close to normal as possible, without frequent occurrence of hypoglycemia. All individuals should strive for targets in accordance with current ADA recommendations, with HbA1C levels of less than 7% in adults and less than 7.5% in adolescents (age 12–17 years), and with preprandial glucose levels of 90–130 mg/dL (plasma), postprandial levels of less than 180 mg/dL, and bedtime levels of 110–150 mg/dL.

All participants will be expected to take a sufficient number of daily insulin injections to meet the glycemic targets. In general, the expectation is that all participants will receive at least three injections of insulin daily, including short- and long-acting insulin preparations, or will utilize continuous subcutaneous insulin infusion (CSII insulin pump). Glucose levels should be checked at least four times daily.

After reviewing these records, the diabetes management team will contact the treating physician about possible adjustments in the insulin regimen, referral to a registered dietitian, or other approaches that the diabetes management team believes would improve the glucose control if necessary. Records of glucose measurements and communication with the participant will be kept as source documentation.

Participants will be contacted by the diabetes educator every 2 weeks between visits to assess their diabetes. In addition, insulin use and hypoglycemic events will be captured at each visit on the appropriate CRFs. Participants will be required to record the amount of insulin they have used during the 5-day period immediately preceding each study visit. Insulin use logs will be provided to participants at each study visit and collected at the next visit. These logs will serve as the source documents.

5.19 Withdrawal from Study Medication

5.19.1 Scheduled Withdrawal from Study Medication

Once a participant reaches Visit 5, all study drug administration should be completed. The site should follow these procedures:

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

5.19.2 Unscheduled Withdrawal from Study Medication

Study medication according to study specifications will be discontinued for an individual participant if *any* of the following occurs:

- A discontinuation criterion for ATG or GCSF is met.
- Pregnancy occurs.
- A severe or serious AE occurs, which, based on the medical judgment of the investigator, prevents a participant from completing the study treatment (see section 8 for classification of AEs).
- The investigator determines that it is in the participant’s best interest to discontinue treatment.
- The participant, or participant’s legal representative, requests that treatment be halted.

Please note: The site must inform the Protocol Chair, the Medical Monitor, and the TNCC if a participant is withdrawn from study medication if any of the criteria listed above occurs.

A participant who is withdrawn from study medication should still continue to be followed on the study and continue with follow-up visits as outlined above. If a participant is withdrawn from study medication the site should follow these procedures:

- Step 1. Complete the “Change of Study Drug” PRN eCRF in the online electronic data capture system and indicate that study medication has been discontinued.
 - a. The “Date of Visit” should be the date the coordinator determined the participant is no longer taking study drug.
 - b. The “Date change in study drug status effective” should reflect the date the subject was discontinued from taking study medication.
 - c. Indicate the reason the participant discontinued study drug.
- Step 2. If participant agrees to continue with study visits the site should continue with follow-up visits and assessments as scheduled.

- Step 3. If the participant no longer wants to participate in the study, please follow procedure outlined in section 5.18.4.

5.20 End of Study Participation

5.20.1 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.

5.20.2 Participant Randomized in Error

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

5.20.3 Lost to Follow-Up and Withdrawal from Study Medication

This study utilizes an intent-to-treat design in which all subjects randomized into the study should continue all scheduled follow-up assessments until the time of death or the declared end of the study. Participants who are withdrawn from study medication will continue to be followed on the protocol. Participants who are lost to follow-up may return to the study at any point if the study is still in active follow up. Noncompliance with taking study medication or missing study visits does not eliminate participants from the trial.

5.20.4 Participant Withdrawal or Lost to Follow-up

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

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

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

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

5.20.5 Participant – Determining Lost to Follow Up

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

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

5.20.6 Reactivation into the Study

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

- Step 1. Complete a "Change of Status" PRN eCRF in the online electronic data capture system and indicate that the participant is being reactivated.
 - a. The "Date of Visit" should be the date of the participant's first visit after rejoining the study.
 - b. The "Date change in status became effective" should reflect the date it was determined that the subject rejoined the study.
 - c. Proceed to section C, enter the date of the subject's first visit rejoining the study.
 - d. The subject will rejoin the study according to the time point at which he/she would currently be due if the subject had remained on the study (based on date of randomization). For example, if a participant left the study at Visit 4 (Week 8) and decided to return 13 weeks later, the next expected visit – and therefore procedures to follow- would be Visit 7 (Week 24).
- Step 2. If the participant decides to continue study drug, then the site should complete the "Change of Study Drug" PRN eCRF in the online electronic data capture system and indicate that the participant is re-starting study medication.
 - a. The "Date of Visit" should be the date of the participant's first visit after rejoining the study.
 - b. The "Date change in study drug status effective" would be the date the participant re-started study medication.

5.20.7 Permanent Study Discontinuation (Study Drug and Follow-Up)

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

5.20.8 Maximum Follow-up Reached (Visit 11)

When the maximum follow up has been reached, the site should follow these procedures for participants enrolled at the site:

- Step 1. Once the participant has undergone the last scheduled visit according to the Schedule of Events, enter data from source document into the online eCRF (all applicable fields).
- Step 2. Complete a Change of Status form in the online data capture system indicating the participant is becoming inactive.
 - a. The reason would be "Maximum follow-up reached".

5.20.9 Death

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

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

5.21 Missed Visits/Visits Occurring Outside Window

5.21.1 Missed Visit

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

- Step 1. For that visit time point, under "Tracking" select "Not Done" for all forms.
- Step 2. Complete one Protocol Deviation form indicating that the visit was missed.
- Step 3. Document the reason for the missed visit in the source.

5.21.2 Visit Occurs Outside of Allowed Window

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

- Step 1. For that visit time point, complete the visit e-CRF's using the correct visit forms (For example, if Visit 5 (Week 10) occurred 5 days after the allowable window, the visit will still be entered onto the Visit 5 (Week 10) visit forms.
- Step 2. Complete one Protocol Deviation form indicating "Entire study visit completed outside visit window".

5.21.3 Missed or Incomplete Specimen Collections

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

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

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

6. INSTRUCTIONS FOR PARTICIPANT TRANSFER AND REMOTE STUDY VISITS

6.1 Participant Transfer

6.1.1 Originating Site Procedures

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

- Step 1. Contact the TNCC and notify them of the proposed participant transfer.
- Step 2. Determine the most suitable new site for the participant. This can be done by navigating to the member directory and searching for sites by zip code or city. You may also go to IRB Approved Sites under “Contacts” on the Website Homepage, as shown below:



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

Step 8. Notify the new site that the participant has been transferred in the online system.

6.1.2 New Site Procedures

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

6.2 Remote Participant Visits

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

Sites should not transfer participants to a site that is not approved for the study. No study procedures, including specimen collections, can be performed at an unapproved site.

7. Informed Consent

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

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

7.1 Required Elements of Informed Consent

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

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

- 2) A description of any reasonably foreseeable risks or discomforts to the subject.
- 3) A description of any benefits to the subject or to others which may reasonably be expected from the research.
- 4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- 5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.
- 6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- 7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- 8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

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

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

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

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

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

7.1.1 Assent of Children

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

7.1.2 Consent for Stored Samples

Participants will be asked to provide consent for long-term storage of any remaining blood samples in the NIDDK Repository after TrialNet is over. (Note: those who decline to have their samples stored after TrialNet is over can still participate in the TN19 Study.)

However, in order to participate in the TN19, participants are required to provide consent for stored samples while TrialNet is ongoing. Participants have the right to withdraw their consent to store samples while TrialNet is ongoing and to have their stored samples destroyed to the extent possible. However, the participant may no longer continue in the TN19 Study.

Purpose: At the Screening, Baseline, and Follow-up Visits, samples may be drawn for future studies to characterize how ATG-GCSF alters general and diabetes-specific immune responses, gain a better understanding of the mechanism of action for ATG-GCSF in the maintenance of β -cell function and determine whether the loss of tolerance associated with this disease is reversed, and assess effects of ATG-GCSF on insulin sensitivity. The total blood draw volume in adults is no more than 10.5 mL/kg or 500 mL in an eight week period, whichever is smaller. For children, no more than 5 mL/kg will be drawn at any single visit and no more than 9.5 mL/kg over an eight week period.

7.2 Informed Consent Process

7.2.1 Administration of the Informed Consent Process

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

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

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

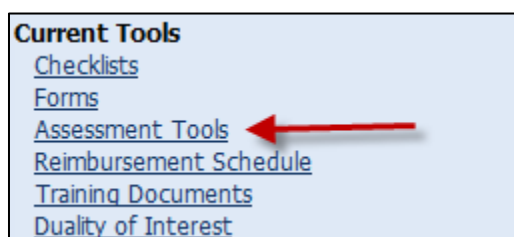
Source: <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126431.htm>

7.2.2 Documentation of the Informed Consent Process

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

1. Standard Operating Procedure (SOP): Sites may create an SOP to be filed in the study regulatory file which outlines the sites' process of obtaining informed consent.
2. Informed Consent Process Checklist: Site may create a checklist outlining all informed consent procedures to be included in each individual subject chart.

The TNCC has created a template consent process statement and template checklists which conform to these guidelines. The templates are located on the member's website in the TN19 protocol home page under Assessment Tools:



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

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

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

8. Data Management

8.1 Introduction

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

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

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

Please Note: For a list of current definitions, please refer to Appendix A.

8.2 Protocol Tool Management

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

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

8.3 System Requirements

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

Hardware and software:

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

General considerations when using a web-based system:

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

8.4 International Considerations

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

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

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

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

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

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

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

9. Online Data Capture System

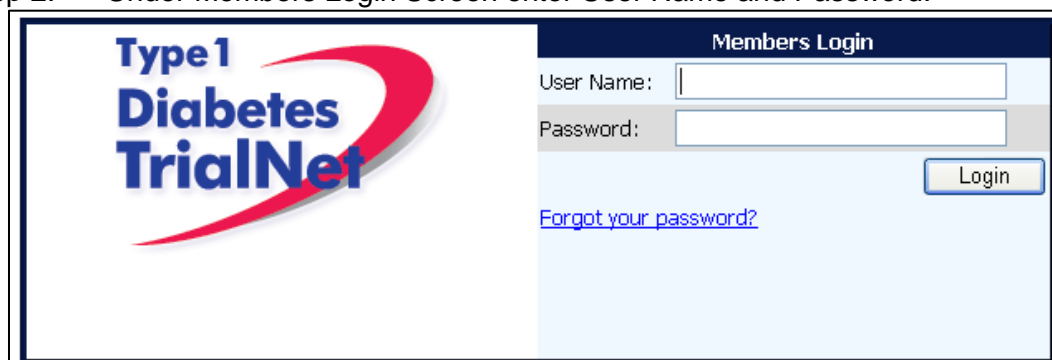
9.1 Overview and Basic Functionality

9.1.1 Login/Navigate to the TN19 Protocol Manager Area

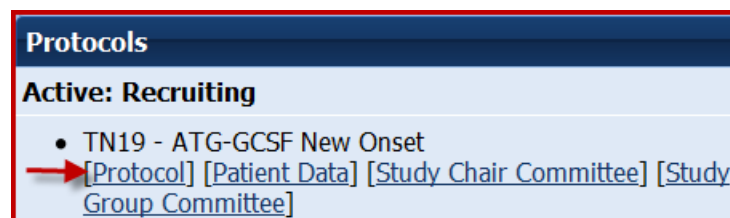
Step 1. Procedure to login and navigate to the TN19 protocol manager area: Log into TrialNet Members Site: <http://www.diabetestrialnet.org/members.htm>.



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



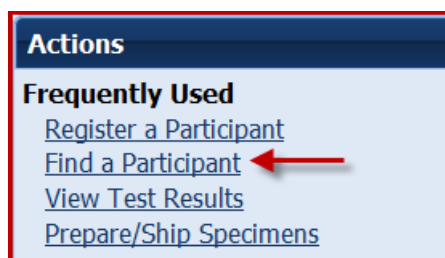
Step 3. Navigate to the "Protocols" portlet. Under TN19, select "Protocol."



9.1.2 Finding a Participant

Note: This procedure will be done for every visit.

Step 4. Procedure to find participant: Once in TN19 Protocol, navigate to the "Actions" portlet and select "Find Participant."



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

Search Advanced Search

Find a Participant

Local ID:

Participant ID:

OR

Site:

Step 6. The list of subjects matching entered criteria will populate below the search box. Click on Local ID (in blue text color). This will open the Participant Detail Screen

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

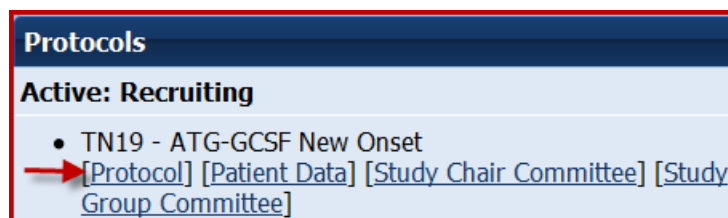
Page 1 of 1

Total Records: 4

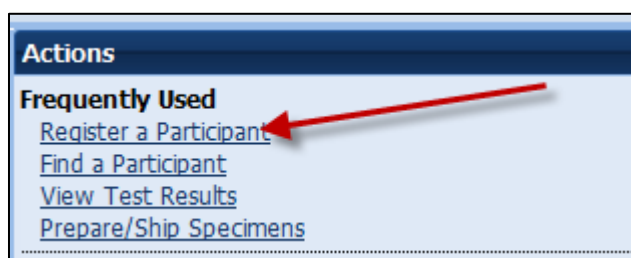
[\[First Page\]](#) [\[Previous Page\]](#) [\[Next Page\]](#) [\[Last Page\]](#)

9.1.3 Registering a Participant

- Step 1. Log into TrialNet Members Website and navigate to the Protocols portlet. Select the “Protocol” link under TN19- ATG-GCSF New Onset Study.



- Step 2. Once in TN19 Home Page, navigate to the Actions portlet and select “Register Participant.”



- Step 3. Once the Register Participant Screen is displayed complete the following fields
- Local ID: The site can enter the desired local ID for the participant. This can include numbers and letters.
 - Letters: Enter three letters.
 - Participant ID: ID should remain the same for interventional studies
Note: PID should be skipped if first time participant on TrialNet study.
 - Site: Select applicable site.
- Step 4. Click on the Register Participant. A success message with the auto-generated Participant ID will appear. For example :

Register a Participant	
Local ID:*	Site creates Local ID
Letters:	Any three letter code assigned by the site to identify an individual
Participant ID: (Enter only if you wish to register a participant that has already been registered on a different protocol.)	
Site:	Click arrow to select your site
Select after entering Local ID, Letters and Site	
Register Participant	

You have successfully registered Participant ID : 100308

- Step 5. Record the Participant ID for your source documents.
- Step 6. If you want to view the participant details for the newly registered subject, select the “Participant Details” button at the bottom of the “Register a Participant” box.

Register a Participant

Local ID: * 2009030101

Letters: * ABC

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

Site: University of Miami [6]

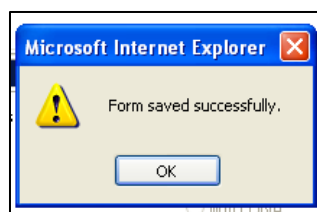
You have successfully registered Participant ID : 100308

Participant Details Register Participant

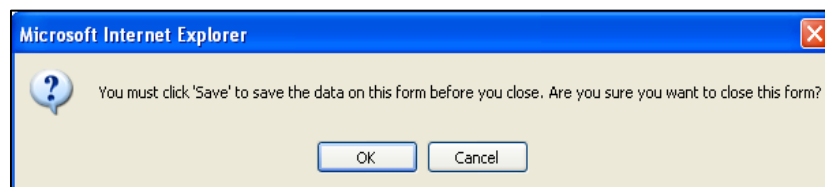
9.1.4 Save and Close e-CRFs

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

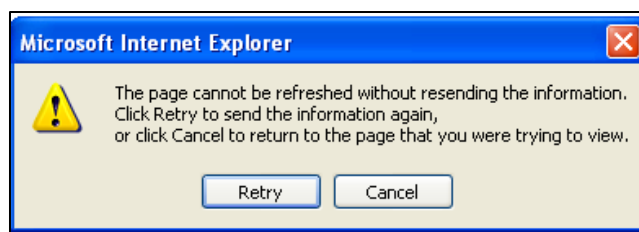
- Step 1. Procedure to save and close-out form: After entering the data select “Save”. The message “Forms saved successfully” will display.



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



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



9.1.5 Save and Close Specimen Collection Forms

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

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

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

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

9.1.6 Form Required Fields

There are two kinds of required fields on every form:

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

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

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

9.1.7 Clear ALL Data from a Form

If you find you have mistakenly entered incorrect 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.

→ **Clear Form**

Protocol # TN19 - ATG-GCSF New Onset

Participant ID: 123456	Date of Registration: 05 Sep 2014
Local ID: JM123456	Letters: JLM
Status: Eligible	Date of Baseline Exam: 05 Sep 2014
Site: Benaroya Research Institute [10]	

Screening Visit Assessment Form

Page: 1 of 6

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

Date of Visit: * 5 Sep 2014 [Date](#)

Interviewer User ID: * 55585

A. DEMOGRAPHIC INFORMATION

- 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: TN19_ScreeningVisitAssessment

Form Cd: 212233

History Type: Subject History

History Id: 1353767

- 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."

Message from webpage

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:	TN19_ScreeningVisitAssessment
Form Cd:	212233
History Type:	Subject History ▼
History Id:	1353767
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

TN19 - ATG-GCSF New Onset

Participant's Details

Timepoint	Event Title	Tracking	Event Status
Screening	Registration Form		Complete
	Screening Eligibility Form		Complete
	Screening Visit Assessment Form		Complete
	CBC with Differential	Tracking	
	Concomitant Medications	Tracking	
	Urinalysis Evaluation Form	Tracking	
	Screening Specimen Collection	Tracking	

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

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

9.3 Data Entry for Visit Forms

9.3.1 Screening Eligibility Form

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

Step 2. Under Event Title, select “Screening Eligibility”.

Timepoint	Event Title	Tracking	Target Date	Due Date	Last Modified Date	Event Status
Screening	Registration Form		15 Aug 2014	15 Aug 2014	15 Aug 2014	Complete
	Screening Eligibility 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.

- a. Review all Inclusion criteria
- b. Review all Exclusion criteria

Please Note: Trial Coordinators should stop and review the medication exclusion criteria from the protocol.

c. Consent Option

- i. Date written informed consent obtained: Record the date that the participant signed the Informed Consent Form.
- ii. On the consent form, did the participant give permission to store samples for future testing after TrialNet is over: Select the bubble corresponding to each response the participant gave on the informed consent form:

Step 5. After entering data, please reference section 9.1.5 Save and Close e-CRF form.

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

Please Note: Once the Screening Eligibility form is complete and participant is eligible for the study, the Baseline Eligibility Form will populate for the participant.

9.3.2 Data Entry for Screening Visit Assessment Form

Step 6. Be sure the Source Document is completed prior to completing forms

Step 7. Under Event Title, select "Screening Visit Assessment".

Screening Visit Assessment	Tracking
--	--------------------------

Step 8. Once the form displays, enter Date of Visit and your Interview User ID.

Protocol # TN19 - ATG-GCSF New Onset

Participant ID:	123456	Date of Registration:	15 Aug 2014
Local ID:	JM0001	Letters:	KEA
Status:	Eligible	Date of Baseline Exam:	15 Aug 2014
Site: Benaroya Research Institute [10]			

Screening Visit Assessment Form

Page: 1 of 6

MULTI-PAGE FORM

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

Date of Visit: * 15 Aug 2014 [Date](#)

Interviewer User ID: * 54538

A. DEMOGRAPHIC INFORMATION

1. Date of Birth * 01 Dec 2001

2. Sex * ☒ Male ☐ Female

3. Ethnicity * ☒ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Unknown

☐ American Indian/Alaska Native

4. Race: * (check all that apply) ☒ Asian

☐ Black/African American

☐ Native Hawaiian/Other Pacific Islander

☐ White

☐ Unknown/Not Reported

☐ Refused

Complete entire form by using navigation arrows to proceed to next page.

Save Print Close Window

- Step 9. Complete all sections of the form. Please note this is a 6 page form. Use the navigation arrows located at the bottom of the form to navigate to the next page.
- Demographic Information
 - Date of Birth
 - Sex of participant
 - Ethnicity
 - Race
 - Medical History
 - Physical Assessments
 - Pregnancy Monitoring (If applicable)

Step 10. After entering data, please reference section 9.1.5 Save and Close e-CRF form.

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

9.3.3 Concomitant Medications

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

Please Note: Insulin use is captured on the Diabetes Management Case Report Form and should not be included on the Conmed eCRF.

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

Concomitant Medications	Tracking
---	--------------------------

- Step 2. Complete all sections for each medication listed.
- Step 3. This form should be updated at every visit with any additional medications the participant takes including any prescription and over the counter medications.

Please refer to Appendix F for additional instructions on how to complete the concomitant medication form.

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

9.3.4 Specimen Collection Form: Main Collections

Each visit will have one Specimen Collection Form. The form will be limited to only those samples required for that particular participant during that specific visit. Main collections include all specimens except for tolerance collections. Tolerance collections include MMTTs.

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

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

9.3.5 Specimen Collection Form: Tolerance Collections

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

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

- Step 1. After completing the Main Collections navigate to the “Tolerance Collection” by selecting the “Tolerance Collection” tab.
- Step 2. Please refer to the TrialNet Specimen Management System User Manual for additional information regarding completion of Specimen Collection forms.

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

9.3.6 CBC with Differential Results Form

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

CBC with Differential Results	Tracking
---	--------------------------

- Step 2. Complete all sections for each test result listed.
- Step 3. After entering data, please reference section 9.1.5 Save and Close e-CRF form.

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

9.3.7 Urinalysis Evaluation Form

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

Urinalysis Evaluation	Tracking
---------------------------------------	--------------------------

- Step 2. Complete all sections for each test result listed.
- Step 3. After entering data, please reference section 9.1.5 Save and Close e-CRF form.

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

9.3.8 Baseline Eligibility Form

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

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

- a. To document eligibility of autoantibody, MMTT, and all other screening labs, it is recommended to print a copy of the subject's "View Test Results" record and sign/date the print-out for inclusion in the subject's record.
- Step 2. Under the Event Title, select Baseline Eligibility. When the form displays, enter Date of Visit and your Interview User ID.

Baseline Eligibility	Tracking
--------------------------------------	--------------------------

Step 3. Complete all pages of the form.

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

Participant's Details			
Protocol # TN19 - ATG-GCSF New Onset...			
Participant ID:	123456	Date of Registration:	15 Aug 2014
Local ID:	JM0001	Letters:	KEA
Status:	Eligible		
Site:	Benaroya Research Institute [10]		

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

9.3.9 Randomizing Participant/Treatment Assignment

- Step 1. The **Baseline Eligibility form must be complete** and the subject must be eligible prior to assigning treatment to the subject. **Please confirm subject eligibility with the TN19 Protocol CRA prior to randomizing any subject in the system.**
- Step 2. Under the Actions portlet on the Homepage 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 3. A box will open titled Assign Treatment to Participant; enter both the Local ID and Participant ID.
- Step 4. Select Assign Treatment.

Step 5. A message will reflect Treatment Assignment Successful and the Randomization number will be provided. For example:

Note: Each randomization number will only be assigned once.

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

Step 7. The initial order of treatment kits and study supplies must be requested by the infusion site research site pharmacist by completing the Agent Request Form and faxing it to the protocol CRA at the TNCC. Please refer to the TN19 Pharmacy Manual of Operations for additional details regarding initial and subsequent study drug ordering.

9.3.10 Treatment Start Date

After initial study drug infusion-Enter this date in the treatment start date eCRF.

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

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

Step 3. Enter the date the participant began treatment.

Step 4. After entering data Save and Close eCRF

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

9.3.11 Baseline Visit Assessment Form

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

Step 1. Under Event Title, select “Baseline Visit Assessment”.

Baseline Visit Assessment	Tracking
---	--------------------------

Step 2. Once the form displays, enter Date of Visit and your Interview User ID.

Step 3. Complete all sections of the form. Please note this is a 4 page form. Use the navigation arrows located at the bottom of the form to navigate to the next page.

- a. Physical Assessments
- b. Pregnancy Monitoring (If applicable)
- c. Tanner Stage (if applicable)

Step 4. After entering data, please reference section 9.1.5 Save and Close e-CRF form.

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

9.3.12 Diabetes Management Form

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

Diabetes Management	Tracking
-------------------------------------	--------------------------

Step 2. Complete all sections of the form.

Step 3. After entering data, please reference section 9.1.5 Save and Close e-CRF form.

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

9.3.13 Study Drug Form

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

Study Drug	Tracking
----------------------------	--------------------------

Step 2. Complete all following sections on this form:

- i. Section A: Study Drug Administration Criteria
 - a. Answer questions 1-5 (question #1 if female only)
- ii. Section B: ATG Study Dosing Information
 - a. Enter weight in kg
 - b. Enter dose in mg (Dose for Infusion 1= Dosing weight x 0.5mg/kg and Dose for Infusion 2= Dosing weight x 2.0mg/kg)
- iii. Section C: ATG Study Drug Administration
 - a. Record all infusion timepoints including; blood pressure, temperature, heart rate and respiratory rate. Timepoints should be recorded every 30 minutes for the first 2 hours, and then every hour thereafter for 12 hours of infusion 1 and 8 hours for infusion 2.
- iv. Infusion Related Problems
 - a. If participant **DID** experience problems during study drug administration-record the events listed as a-k on study drug form.
- v. Section E: GCSF Administration
 - a. Answer questions 1 and 2, and record any problems subject may have experienced during injection under a-i of the form, including the grade 1-4.
- vi. Section F: Acetaminophen, Methylprednisone, and Diphenhydramine Administration
 - a. Answer questions 1-4.

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

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

9.3.14 Visit Assessment Form

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

Step 2: Under Event Title, select "Visit Assessment".

Visit Assessment	Tracking
----------------------------------	--------------------------

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

Step 4: Complete all sections of the form. Please note this is a 3 page form. Use the navigation arrows located at the bottom of the form to navigate to the next page.

- a. Anthropometrics (if applicable)
- b. Vital Signs (ALL participants)
- c. Pregnancy Monitoring (if applicable)
- d. Tanner Stage (if applicable)
- e. Physical Assessments (ALL participants)

After entering data, please reference section 9.1.5 save and Close e-CRF form.

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

9.4 PRN Forms

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

9.5 List and Definitions of PRN Forms

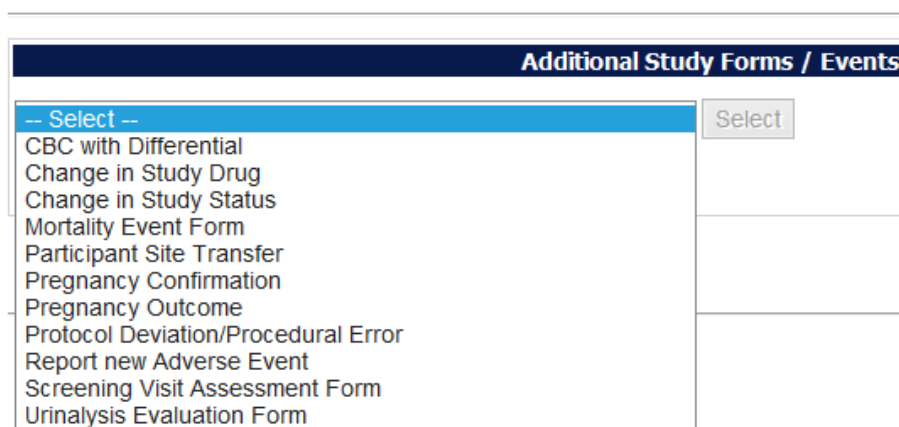
Forms available are as follows:

1. CBC with Differential Results - to be used if an unscheduled visit is completed outside of the normal visit schedule
2. Screening Visit Assessment - to be used if a participant is rescreened for the study
3. Visit Assessment Form – to be used if an unscheduled visit is completed outside of the normal visit schedule
4. Urinalysis Evaluation - to be used if an unscheduled UA is completed outside of the normal visit schedule
5. Change in Study Drug – to be used whenever the participant's study drug use status changes (i.e. voluntary or involuntary withdraw from medication, drug modification, etc)
6. Mortality Event – in the event that a participant fatality occurs during the course of the study, the Mortality Event Report is completed regardless of the cause of death. Information is collected on the date of death, characteristics of the event, and the cause(s) of death.
7. Pregnancy Confirmation – this form is completed in the event that a female study participant becomes pregnant at any point during the course of the study. The form is meant to capture information on the pregnancy including: expected delivery date, discontinuation of study drug, willingness to continue with follow-up visits, and pregnancy history. The form also inquires as to whether the participant has contacted her obstetric care provider regarding her participation or her partner's participation in this study.
8. Pregnancy Outcome – This form is completed when the outcome of a pregnancy is known. It is meant to capture information on the outcome of the pregnancy, most importantly if the pregnancy resulted in a live birth, neonatal death, stillbirth, miscarriage, or an induced abortion, as well as the details of the outcome. If the pregnancy resulted in a live birth, information on the infant is collected. Some responses on this form, if chosen, indicate the completion of an Adverse Event report.
9. Change in Study Status – to be used when the status of a participant changes (subject withdrawals from study or is lost to follow up, etc). Once participants are enrolled in the study, they are enrolled for the duration of the study. A change of status could involve the participant becoming inactive by not being able or willing to attend future follow-up visits. This form will also be completed if an inactive participant decides to return to active study participation by attending future follow-up visits. This form will collect information on the date of the change in status, as well as the reason for the change in status. Note that this form is completed each time a participant changes study status.
10. Protocol Deviation – to be used whenever a protocol deviation occurs (visits or samples are missed or completed outside of allowable visit window, etc). A separate form must be completed for every unique protocol deviation that occurs, even if the subject is the same. The form obtains specific information on the deviation that has occurred, including the date the deviation occurred, the specific deviation that has occurred, as well as the reason for the protocol deviation.
11. Participant Site Transfer – to be used if a subject moves from one study site to another. The form collects information on the date the transfer is occurring and the number of the site to which the participant is transferring.

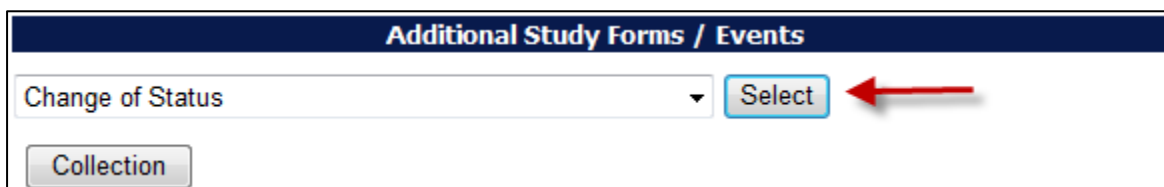
12. Report New Adverse Event – to be used when a subject experiences a reportable adverse event
13. PRN Additional Consent- to be used if a participant's consent option has changed

9.5.1 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.

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

- Step 1. From the participant details page, on the right side of the main screen, directly beneath the subject header, above the study schedule, is a list of all types of PRN forms previously completed for the participant.
- Step 2. Select the type of previously completed PRN form you would like to view

Completed Additional Study Forms
<ul style="list-style-type: none"> • Previous Change of Status • Previous Pregnancy Confirmation

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.

Change in Study Status Form List							
Protocol # TN19 - ATG-GCSF New Onset							
Participant ID:	123456	Date of Registration:	15 Aug 2014				
Local ID:	JM0001	Letters:	KEA				
Status:	Eligible	Date of Baseline Exam:	15 Aug 2014				
Site:	Benaroya Research Institute [10]						
<table border="1"> <thead> <tr> <th>Event date</th> <th>Event Title</th> </tr> </thead> <tbody> <tr> <td>15 Aug 2014</td> <td>Change in Study Status</td> </tr> </tbody> </table>				Event date	Event Title	15 Aug 2014	Change in Study Status
Event date	Event Title						
15 Aug 2014	Change in Study Status						

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

9.5.3 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 serious adverse events and to ease reporting, a standardized classification for adverse events, including a grading scale for severity, will be used. The classification TrialNet utilizes to report adverse events is the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, with the exception of hypoglycemia and hyperglycemia, developed and maintained by CTEP at National Cancer Institute. This classification provides a grade (1-5) to describe event severity.

Throughout the study, only clinically qualified personnel must document occurrence and severity of all adverse events on source documentation. Those that are Grade 2 or greater must be reported on the appropriate adverse event form as described below. The investigator should treat participants with adverse events appropriately and observe them at suitable intervals until the events resolve or stabilize.

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

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

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

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

Data Descriptions:

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

Common Terminology Criteria for Adverse Events (CTCAE):

The values to describe adverse events will come from the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, with the exception of hypoglycemia and hyperglycemia, developed and maintained by CTEP at National Cancer Institute. The CTCAE v.4.0 was chosen because of its widespread use as a standard for adverse event reporting in clinical trials, its specific criteria for grading severity, and its ongoing maintenance from the National Cancer Institute (NCI). Additionally, the NCI has provided mappings from CTCAE to MedDRA, the current standard for FDA reporting.

The CTCAE is organized broadly by categories. Each category is a broad classification of AEs based on anatomy and/or pathophysiology. Within each category, AEs are listed (alphabetically)

accompanied by their descriptions of severity (grade). An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE must be associated with a grade. Grade refers to the severity of the AE. The CTCAE v4.0 displays Grades 1 through 5 with unique clinical descriptions of severity of each AE based on this general guideline:

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

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

Using the CTCAE:

TrilaNet provides several resources for the proper use of CTCAE codes for adverse event reporting. Because the NCI has developed and maintained the CTCAE classification, the recommended educational materials are from the NCI. Each person entering data in the AE system should be given a copy of a small spiral-bound booklet titled "Common Terminology Criteria for Adverse Events (CTCAE), version 4.0." [NIH Publication No. 03-5410.] This booklet contains the entire CTCAE, with descriptions of each event and grade.

Additionally, the CTCAE can be accessed online from the NCI at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

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

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

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

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

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

Note: Grade 5 is the only appropriate Grade for the Death Category. This AE is to be used in the situation where a death: 1.) cannot be reported using a CTCAE v4.0 term associated with Grade 5, or 2.) cannot be reported within a CTCAE category as 'Other (Specify)'.

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

The NCI also posts an Index to the CTCAE at:

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

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

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

10.2 Reporting Timeline

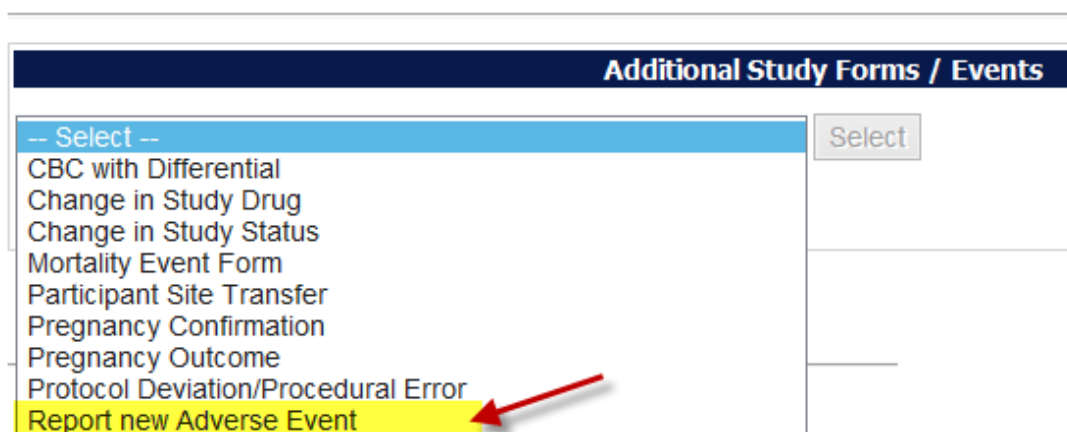
Follow the timelines below for the reporting of adverse events:

- Within **24 hours** (of learning of the event), investigators must report any Serious Adverse Event (SAE) that:
 - Is considered life-threatening/disabling or results in death of subject
 - OR-
 - Is Unexpected/Unanticipated
- Investigators must report all other SAEs within **5 working days** (of learning of the event).
- All other (suspected) grade 2 or greater AEs must be reported to the TNCC within **20 working days** of the notification of the event or of the site becoming aware of the event.

10.3 Directions for Reporting AE's / System Description

10.3.1 Navigating to the Adverse Event Form

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



Additional Study Forms / Events

-- Select --

- CBC with Differential
- Change in Study Drug
- Change in Study Status
- Mortality Event Form
- Participant Site Transfer
- Pregnancy Confirmation
- Pregnancy Outcome
- Protocol Deviation/Procedural Error
- Report new Adverse Event**

Select

10.3.2 Reporting an Adverse Event

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

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

Adverse Event Reporting – Description of each field:

Section A. Interview Information:

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

Initial Report

* These fields are required in order to SAVE the form

A. INTERVIEW INFORMATION

Adverse event report date (DD MMM YYYY) *

Section B. Adverse Event Report

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

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

B. ADVERSE EVENT REPORT

Adverse event occurrence date (DD MMM YYYY) *

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

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

Is this a primary or secondary event?

☒ Primary ☐ Secondary* (required only for initial report)

If secondary event, enter primary Adverse Event ID:

Section C: Event Description

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

C. EVENT DESCRIPTION

Event Category *Help

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

Event Supra-term "Type of Event"

*

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

Event Select "Site or Modifier"

* (required only if options are present in drop down list)

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

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

Severity	▼ *
----------	-----

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

Note: Do not indicate PHI including gender of participant.

For Example:

Not Acceptable: “He developed a rash.”

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

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

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

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

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

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

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

Patient status (at time of report):	<div style="border: 1px solid black; height: 20px; position: relative;"> ▼ * </div>
-------------------------------------	---

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

Adverse event resolved date	<div style="border: 1px solid black; padding: 2px;"> <div style="display: flex; align-items: center;"> <div style="border: 1px solid black; width: 40px; height: 20px; position: relative;"> ▼ </div> <div style="margin-left: 10px;">(DD MMM YYYY)</div> </div> </div>
-----------------------------	--

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

Date of death	<div style="border: 1px solid black; padding: 2px;"> <div style="display: flex; align-items: center;"> <div style="border: 1px solid black; width: 40px; height: 20px; position: relative;"> ▼ </div> <div style="margin-left: 10px;">(DD MMM YYYY)</div> </div> </div>
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- Additional Comments: Add any additional pertinent information that is not captured elsewhere on the form.

Additional comments	<div style="border: 1px solid black; height: 50px; position: relative;"> Provide additional information if not captured elsewhere on the form </div>
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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)
<div style="border: 1px solid black; padding: 2px;"> <div style="display: flex; align-items: center;"> <div style="border: 1px solid black; width: 40px; height: 20px; position: relative;"> ▼ </div> <div style="margin-left: 10px;">(DD MMM YYYY)</div> </div> </div>	<div style="border: 1px solid black; padding: 2px;"> <div style="display: flex; align-items: center;"> <div style="border: 1px solid black; width: 40px; height: 20px; position: relative;"> ▼ </div> <div style="margin-left: 10px;">(DD MMM YYYY)</div> </div> </div>
<div style="border: 1px solid black; padding: 2px;"> <div style="display: flex; align-items: center;"> <div style="border: 1px solid black; width: 40px; height: 20px; position: relative;"> ▼ </div> <div style="margin-left: 10px;">(DD MMM YYYY)</div> </div> </div>	<div style="border: 1px solid black; padding: 2px;"> <div style="display: flex; align-items: center;"> <div style="border: 1px solid black; width: 40px; height: 20px; position: relative;"> ▼ </div> <div style="margin-left: 10px;">(DD MMM YYYY)</div> </div> </div>
<div style="border: 1px solid black; padding: 2px;"> <div style="display: flex; align-items: center;"> <div style="border: 1px solid black; width: 40px; height: 20px; position: relative;"> ▼ </div> <div style="margin-left: 10px;">(DD MMM YYYY)</div> </div> </div>	<div style="border: 1px solid black; padding: 2px;"> <div style="display: flex; align-items: center;"> <div style="border: 1px solid black; width: 40px; height: 20px; position: relative;"> ▼ </div> <div style="margin-left: 10px;">(DD MMM YYYY)</div> </div> </div>
<div style="border: 1px solid black; padding: 2px; display: inline-block;">Add</div>	

- 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:

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

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

Reporter Information:

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

REPORTER INFORMATION
Reporter User ID <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.

Save Draft	Submit for Review	Print	Close Window
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Please Note: Contact TNCC CRA if there are any additional questions regarding this form

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

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

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

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

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 visit date when the participant resumed study treatment. For instance: Participant 123456 missed visit 3 and visit 4 for any reason, but resumed treatment at visit 5 (date 4/11/2011) then the next **Start Date** entered would be 4/11/2011.

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

Step 1. 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 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 followup: Select reason for follow-up

Reason for followup	<input type="text"/> *
<div> Additional information requested by the medical monitor Correction of initial report New information, progression of event </div>	

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

Save Draft	Submit for Review	Print	Close Window
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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 form will be available to investigators and delegated personnel at all study sites. As with all other aspects of TNCC-provided protocol management tools, the Adverse Events Data Management System is a secure web site with password access.

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

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

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

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

10.6 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.

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

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

The process for reporting to the FDA is as follows:

1. Site completes 3500A MedWatch report (mandatory reporting form).

- f. Link to form and Instructions for completing the form can be found on the FDA Website.
 - g. It is up to the site to determine if a MedWatch SAE should be completed
 - h. Site emails completed 3500A MedWatch report to TNCC CRA and TrialNet Medical Monitor (Brett J. Loechelt, MD; bloechel@cnmc.org)
2. Within 15 calendar days (or 7 calendar days if fatal or life-threatening**** suspected adverse reaction)**** of being notified of the event, the TNCC sends the 3500A MedWatch report to FDA
 - i. FDA recommends the sponsor notify FDA by telephone, email or facsimile transmission prior to submitting the MedWatch Report.

***FDA believes that the sponsor is better positioned than the individual investigator to assess the overall safety of the investigational drug because the sponsor has access to serious adverse event reports from multiple study sites and is able to aggregate and analyze these reports. For this reason, investigators must immediately report any serious adverse event to the sponsor, without regard to causality (21 CFR 312.64(b)). However, it is also important for the sponsor to consider the investigator's view when assessing the safety of the drug and determining whether to report expeditiously to FDA because the investigator is knowledgeable about the human subject (e.g., medical history, concomitant medications), administers the investigational drug, monitors the subject's response to the drug, is aware of the subject's clinical state and thus may be sensitive to distinctions between events due to the underlying disease process versus events that may be drug-related, and may have observed the event.

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

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

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

*****Under 21 CFR 312.32(c), the sponsor is required to notify FDA and all participating investigators in an IND safety report of potentially serious risks from clinical trials or any other

source, as soon as possible, but no later than 15 calendar days after the sponsor receives the safety information and determines that the information qualifies for reporting.

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

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

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

11. Protocol Manager: Portlets and Tools

From the TrialNet TN19 ATG-GCSF New Onset homepage, there are a series of portlets meant to assist/aid sites in the conduct of the study.

11.1 TN19– Working Documents Portlet

From the TN19 ATG-GCSF New Onset 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](#)
- [Investigator Brochure](#)
- [Informed Consents](#)
- [Certificate of Confidentiality](#)
- IRB Memos**
- [DSMB Letter](#)
- [Questionnaires](#)
- [Volunteer Quiz](#)
- [Volunteer Handbook](#)
- [Recruitment Materials](#)
- [Blood Volume Table](#)

Current Tools

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

Current Manuals

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

Archive

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

11.1.1 **Current IRB Documents**

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

11.1.2 **Current Tools**

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

1. Checklists
 - a. Visit Checklists
 - b. Consent Checklists
 - c. MMTT Checklists
2. Forms
 - a. Pharmacy Forms
 - i. Agent Request Form
 - ii. Clinical Site Contact Form
 - b. Current Site Forms
 - i. FDA 1572 Template
 - ii. Site Activation Checklist
 - iii. Clinical Site Information
 - iv. W-9
 - v. Payment Information Form
 - vi. New User/Correct User/Remove User Form
 - vii. Site Delegation Log
3. Assessment Tools
 - a. Case Report Forms-Template source documents*
 - b. Specimen Collection Forms-Template source documents*
 - * Sites can edit templates or create their own
 - c. Subject File templates
 - i. Subject Files Checklist for FDA-Regulated Studies
 - ii. Adverse Event Log
 - iii. Protocol Deviation Log
 - iv. IGRA Verification Document
 - v. Blood Glucose/Insulin Log
4. Reimbursement Schedule
5. Training Documents
 - a. Training Matrix
 - b. Training Presentations and materials related to the study
 - c. 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. Protocol Manual of Operations (MOO)
2. Pharmacy Manual of Operations
3. Laboratory Manual

4. Specimen Management System (SMS) User Manual

11.1.4 Laboratory References

Under the “Laboratory References” header are the most current versions of general laboratory materials to aid sites in proper specimen handling procedures, including:

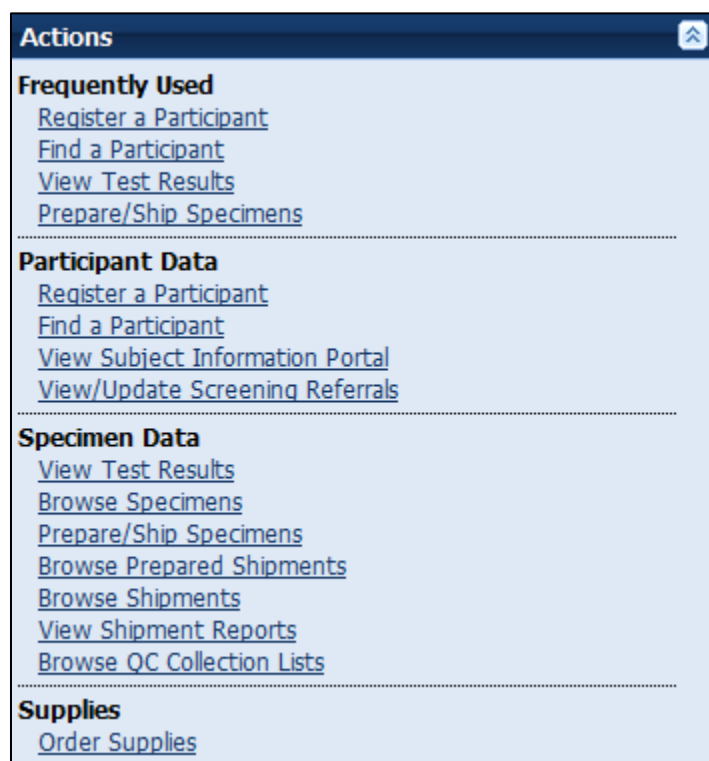
1. Specimen Processing References
 - a. Laboratory Reference Ranges
2. Laboratory Turnaround Time Table
 - a. a. Laboratory Result TAT Table
3. Destruction of Stored Specimens
4. Laboratory Certifications
5. Laboratory Closure Schedule (for current year)

11.1.5 Archive

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

11.2 TN19 – Actions Portlet

From the TN19 ATG-GCSF New Onset homepage, all study-related actions are available in the “Actions” portlet.



11.2.1 TN19- Frequently Used

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

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

11.2.2 Participant Data

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

1. Register a Participant
 - a. This link takes the user to register a new participant for the study.
2. Find a Participant
 - a. This link takes the user to locate a participant’s record.
3. Assign Treatment
 - a. This link takes a user to the “Assign Treatment” page where the user may randomize the participant in the system. Please note: a site should only randomize a participant in the system after the TNCC protocol CRA has confirmed the participant’s eligibility for the study and has directed the site to randomize the participant in the system.
4. View Assigned Treatment Report
 - a. This link takes the user to view all of the assigned treatments for participants at their site.

11.2.3 Specimen Data

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

11.2.4 Supplies

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

11.3 TN19 – Contacts

From the [TN19-ATG-GCSF New Onset](#) homepage, all study-related contacts are available in the “Contacts” portlet.

Contacts
Study Chair/PI Email Dr. Michael Haller
Coordinator Contacts
IRB Approved Sites
TNCC Email Jessica Miller (Primary CRA) Email Nichole Reed (Secondary CRA)

11.4 Administration Portlet

From the TrialNet Member's Website homepage, all administration-related tools are available in the "Administration" portlet.

Administration
Change Password
Complete/Update Duality Form

11.5 TN19 – Clinical Toolkit

From the TN19 ATG-GCSF New Onset homepage, all study-related clinical tools are available in the "Clinical Toolkit" portlet.

Clinical Toolkit
20091215 SMS Emergent Unblinding Flowchart FINAL.pdf

11.6 TN19 – Calendar

From the TN19 ATG-GCSF New Onset homepage, all study-related calls, trainings and event are noted in the "Calendar" portlet.

TN19 - ATG-GCSF New Onset in EDT
Mon Aug 25 2014
Tue Aug 26 2014
Wed Aug 27 2014
Thu Aug 28 2014
Fri Aug 29 2014
Sat Aug 30 2014
Sun Aug 31 2014
Monthly

11.7 TN19 – Protocol Development Committees

From the [TN19 ATG-GCSF New Onset](#) 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

11.8 TN19 – Publications

From the [TN19 ATG-GCSF New Onset](#) homepage, all protocol specific publications, ancillary publications and data sharing policies are located under the “Publications” portlet.

Publications
Protocol Publications
Ancillary/Sub-study Publications
Data Sharing

11.9 TN19 – Frequently Asked Questions

From the [TN19 ATG-GCSF New Onset](#) homepage, all protocol specific frequently asked questions (FAQs) are located under the “Frequently Asked Questions” portlet.

12. Member's Website Reports

12.1 Network Wide Reports

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



Step 2. Select your site folder.

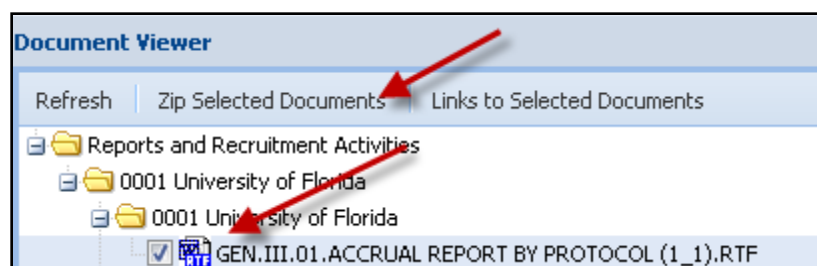
Step 3. Next, select the "General Reports" folder.

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

Network Wide Reports Currently Available:

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

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



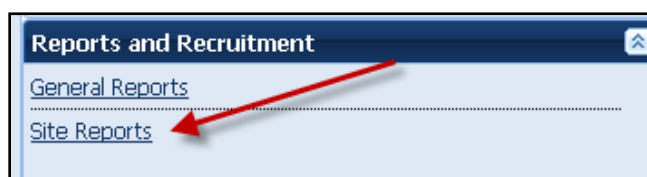
12.2 Protocol Specific Reports

From the TN19 ATG-GCSF New Onset homepage, all general and site specific reports are located under the “Reports and Recruitment” portlet.



12.2.1 Accessing Protocol Specific Reports

Step 1. To access reports with specific data for your individual site, from the TN19 protocol page, navigate to the “Reports and Recruitment” portlet. Select the “Site Reports” link.



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

Step 3. Select the folder for your specific site.

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

Step 5. To open a report, you can click a report title to download a single report or you can select multiple reports to download by selecting the box next to each report

and clicking the button “Zip Selected Documents.” This will download multiple documents to your computer as a zip file.

12.2.2 Protocol Specific Reports Currently Available:

Folder	Report Title	Report Description	Updated
General Reports	TN19.I.01.Accrual Report By Clinical Center.rtf	Accrual totals, by clinical center	Monthly
	TN19.I.02.Actual.v.Expected Accrual - Graph.rtf	Graph of actual verses expected accrual.	Monthly
	TN19.I.03.IRB Summary - Ethnicity, Race and Gender Report.rtf	IRB summary of ethnicity, race and gender for all subjects	Monthly
	TN19.I.04.Adverse Event Summary Report.rtf	Summary of all reported AEs and SAEs	Weekly
	TN19.01. Screening and Enrollment.rtf <u>(if applicable)</u>	Screening and Enrollment report by year <u>(if applicable)</u>	Weekly <u>(if applicable)</u>
Site Reports	TN19.II.01.Accrual Report By Institution (CC#).rtf	Accrual summary for clinical center and all affiliates	Monthly
	TN19.II.02.IRB Summary - Ethnicity, Race and Gender Report (CC#).rtf	IRB summary of ethnicity, race and gender for each site	Monthly
	TN19.III.01.Accrual Report (CC#_Site#).rtf	Displays protocol accrual totals	Monthly
	TN19.III.02.IRB Summary - Ethnicity, Race and Gender Report (CC#_Site#).rtf	Displays IRB summary of ethnicity, race and gender	Monthly
	TN19.III.03.Adverse Event Summary Report (CC#_Site#).rtf	Displays summary of all AEs and SAEs	Monthly
	TN19.III.09.Participant Schedule of Visits Report (CC#_Site #).rtf	Displays a calendar of target dates for subjects' visits	Daily
	TN19.II.16.Screening Report by Month (CC#_Site##).rtf <u>(if applicable)</u>	Displays all screening reports by year and month <u>(if applicable)</u>	Daily <u>(if applicable)</u>

13. SUPPLIES

13.1 Supply Ordering System Overview

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

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

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

13.2 Ordering Supplies

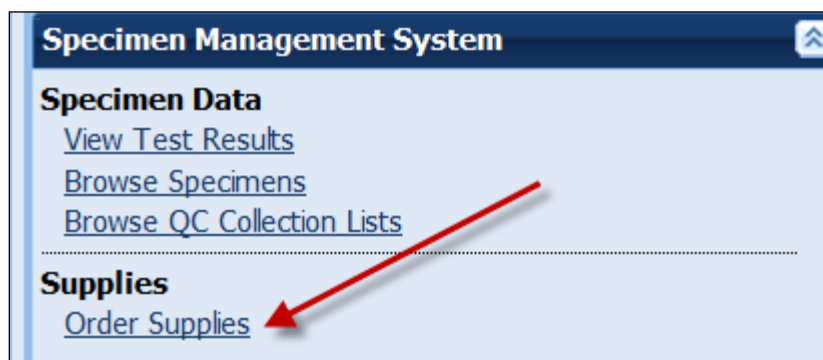
13.2.1 Ordering Study Agent

Please refer to the TN19 Pharmacy Manual of Operations.

13.2.2 Navigating the Fisher BioServices Supply Ordering System (SOS)

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

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




From the TN19 ATG-GCSF New Onset Study homepage, navigate to the central “Actions” portlet and select “Order Supplies.”

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

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

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

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

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

<input type="button" value="Add New Supply Order"/>	<input type="button" value="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:
- 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.”
 - If you do not have any special instructions or comments regarding the order, please select “Skip instructions/Comments Entry and Proceed to Supply Order.”

Order # 18476

[Delete Order](#)

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

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

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

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

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

1

Acknowledge Shipping Site Warning

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

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

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

Acknowledge Shipping Site Warning

2

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

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

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

[Abandon/Delete Order](#)

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

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

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

Contact: [Kelly Sadler](#)

2

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

1

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

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

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

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

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

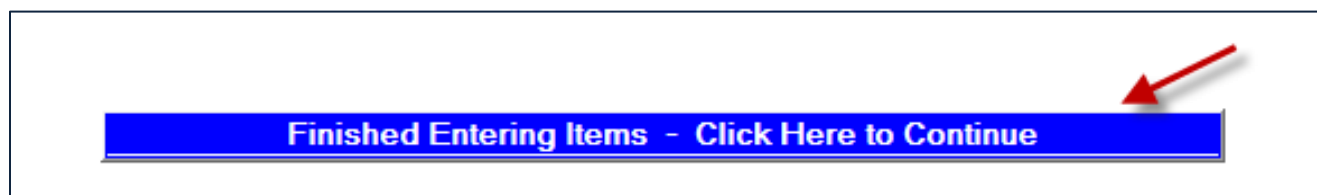
Step 10. Select the supplies you wish to order by placing a checkmark in the “Selected” column and indicating the number of units desired. Please note the packaging units per item when entering the number of units you require. Some items are

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

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

Item #	Item Description	Part #	Catalog #	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			Click to view supply	Explain	50	2	100	0		USF	<input checked="" type="checkbox"/>
PR-00199	2.5 mL Red Top SST Collection Tube with Clotting Activator		Click to viewProduct Description	Click to view supply	Explain	50	1	50	0	31-Oct-2015	Fisher BioServices	<input checked="" type="checkbox"/>

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



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

ORDER FORM SUMMARY (ORDER NUMBER: 17400)

Return to Home Page
Add More Items
Update Units Ordered

Add Comment
Submit Order

Generate Template of the Order Items Below for Future Orders
Display Printer Friendly Order View
OK

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

13.2.3 Supply Organization

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

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

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 viewProduct Description	Click to view supply	Fisher BioServices	0	
PR-00001	PR-00001	Ambient	General	Shipping	Absorbent Pads	250	No	No	Click to viewProduct Description	Click to view supply	Fisher BioServices	0	
PR-00002	PR-00002	Ambient	General	Clinical Supplies	Alcohol Swabs	100	No	No	Click to viewProduct Description	Click to view supply	Fisher BioServices	0	
PR-00003	PR-00003	Ambient	General	Clinical Supplies	Angiocatheter, 20 G (Insyte)	50	No	No	Click to viewProduct Description	Click to view supply	Fisher BioServices	0	31-Oct-2016

The table below lists all filter criteria applicable to the **TN19 ATG-GCSF** Study.

TN19 ATG-GCSF Supply Organization	
“Protocol” Filter Criteria	“Assay” Secondary Filter Criteria
TN19 ATG-GCSF	Autoantibodies CBC CD4/CD8 Chemistries DNA EBV/CMV PCR EBV/CMV Viral Serology Epiontis HbA1c HIV/Hep B/Hep C Mechanistic Serum MMTT – 2 or 4 Hour Urinalysis Whole Blood - PBMC/Plasma Whole Blood - RNA
General Supplies	Clinical Shipping PR Incentive
Study Drug Administration	Blinding Labels for GCSF Syringe 0.2 micron Filtered Extension Set for ATG Infusion

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 

14. TNCC Audit Program

14.1 Components of an Audit Site Visit

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

14.2 Selection of Institutions/Investigators

14.2.1 Observational Studies

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

14.2.2 Prevention and Intervention Studies

All TrialNet interventional studies will be audited.

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

14.3 Audit Teams

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

14.4 Arranging the Audit

1. An audit date mutually convenient to the audit team and the site will be selected.
2. A confirmation email, including the TNCC audit confirmation letter, audit agenda, audit information sheet and TNCC audit guidelines will be sent to the site no less than 30 days in advance of the audit site visit.
3. A list of announced cases will be sent to the site no more than 14 days in advance of the audit site visit
4. The Principal Investigator and a CRA at the institution being audited, who is familiar with the selected cases, must be available on the date(s) selected.

5. The length of an audit depends on the number of cases being reviewed and which areas will be audited (i.e. pharmacy, regulatory compliance, IRB). Audits will usually last between a minimum of 4 hours and a maximum of 2 days.
6. The site is responsible for ensuring that all relevant materials are available for review at the time of the audit.

14.5 Selection of Cases

The TNCC will select all cases for all audits.

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

14.6 Preparation by the Institution being Audited

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

Items that should be provided at the audit include:

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

8. If the drug(s) is not dispensed by a pharmacy at the site but by the study team, the drug ordering, handling and storage procedures must be shown to the audit team.
9. Source documentation should be organized so that auditors can easily identify them.

14.7 Required Documents

14.7.1 Regulatory Documents

Essential documents including:	<ul style="list-style-type: none"> Principal Investigator and sub-investigators' Curriculum vitae Principal Investigator 1572 Proof of Human Subject Protection education training for PI and all research staff handling subject data Site Delegation Log Letters of initial and continuing IRB approval IRB committee composition (roster) Required regulatory authority's(ies') authorization/approval Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) that are locally obtained Certification/accreditation for medical/laboratory/technical procedures/tests at start of the study and updates during the conduct of the study for local labs. Important sponsor and/or TNCC correspondence including: letters, meeting notes, notes of telephone calls Subject identification list – list of all subjects entered on the study with their sequence number Subject screening / identification logs, as applicable
Original IRB submission including:	<ul style="list-style-type: none"> Advertisement(s) to recruit subjects Informed consent Any other written information provided to subjects Study agent Investigator's Brochure or package insert (if request by IRB for submission) Case report forms (if request by IRB for submission)
Protocol amendment submission:	<ul style="list-style-type: none"> Amended protocol Amended informed consent Any other amended written information provided to subjects Amended advertisement(s) Amended case report forms (if request by IRB for submission)
All IRB correspondence including:	<ul style="list-style-type: none"> Annual renewal/continuing reviews Updates to Investigator's Brochure Adverse event reporting Acknowledgement of DSMB reports
Study agent documentation including:	<ul style="list-style-type: none"> Receipts sent with shipment of study agent Study agent accountability logs that reflect log in of study agent shipments Study agent accountability logs that reflect each time study agent is dispensed Study agent accountability logs that reflect return or destruction of unused study agent Sample of label(s) attached to investigational product container(s) (what the subject sees) * Procedures for unblinding trial, if applicable

	<ul style="list-style-type: none"> * Master randomization list, if applicable
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14.7.2 Source Documents

Acceptable source documentation includes, but is not limited to:	<ul style="list-style-type: none"> Laboratory results Quality of Life forms Physician or staff dictation Nursing notes Medication records Consults Hospital, clinic, or office medical records Notes to file TrialNet site research charts Signed specimen shipment logs Subject diaries and/or calendars Food diaries Progress notes Demographic forms Pathology reports Radiology reports Operative reports Worksheets within the medical record charts
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1. Good standard of practice for source documentation includes:
 - a. Subject PID legible on all documents
 - b. All entries are legible and signed by staff
 - c. All entries are made in ink or are typewritten
 - d. Data corrections as follows:
 - i. Do not ablate incorrect information. Use a strike through so that original information is still legible.
 - ii. Write the date that the document is changed.
 - iii. Include initials of the person making the change.
 - iv. If corrected information cannot be inserted so it is legible, insert an addendum page with the correction.
 - v. Reports officially issued by a department such as radiology or pathology may only be changed by that department. Changes must be reflected in an officially issued amended report.
 - vi. Documentation with erasures or use of correction tape/fluid is not acceptable.

14.8 Record Retention

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

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

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

A sponsor shall retain the records and reports required by this part for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2

years after shipment and delivery of the drug for investigation use is discontinued and FDA has been so notified.

14.9 Data Reconciliation

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

14.10 Data Delinquency

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

14.11 Audit Results

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

14.11.1 IRB Documentation / Study Conduct

Major violations include <u>but are not limited to</u> :	<ol style="list-style-type: none"> 1. Protocol never approved by IRB 2. Initial IRB approval documentation missing 3. Inappropriate initial approval by expedited review [45 CFR 46.110 non-compliance] 4. Registration and/or treatment of subject prior to full IRB approval (initiation of study related procedures prior to IRB approval) 5. Registration of subject on protocol during a period of delayed re-approval 6. Reportable adverse events not reported to IRB 7. Lack of IRB approval of a protocol amendment.
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14.11.2 Informed Consent

Omissions of one or more of the elements required by federal regulations 21 CFR 50.25 / 45 CFR 46.116:	<ol style="list-style-type: none"> 1. Statement that the study involves research 2. Explanation of the purposes of the research 3. Expected duration of the subject's participation 4. Description of the procedures to be followed 5. Identification of any procedures which are experimental 6. Description of any reasonably foreseeable risks or discomforts to the subject 7. Description of any benefits to the subject or to others which may reasonably be expected from the research 8. Disclosure of appropriate alternative procedures or courses of treatment (if any) that may be advantageous to the subject 9. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records 10. For research involving more than minimal risk, an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained 11. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject 12. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled
Additional major violations:	<ol style="list-style-type: none"> 1. Omissions of multiple risks / side effects as listed in the model informed consent document and/or in subsequent serious adverse event reports 2. Multiple/cumulative effect of minor problems for a given informed consent
Additional consent form issues:	<ol style="list-style-type: none"> 1. Consent form missing 2. Consent form not signed & dated by subject 3. No documentation that consent was given and the form was signed by the subject prior to protocol-related studies or procedures 4. Consent form is missing signatures 5. Consent form not current IRB-approved version at time of subject enrollment 6. Consent form not protocol-specific 7. Consent form doesn't include updates or information as required by IRB 8. Consent obtained in wrong language

14.11.3 Subject Case Records:

Eligibility:	<ol style="list-style-type: none"> 1. Protocol specific eligibility requirements not met 2. Missing source documentation of eligibility requirements
Treatment administration:	<ol style="list-style-type: none"> 1. Incorrect study agent/treatment used 2. Additional agent used which is not permitted by that protocol 3. Dose calculated incorrectly 4. Dose modifications not justified 5. Treatment doses incorrectly administered, calculated or documented
Toxicity:	<ol style="list-style-type: none"> 1. Failure to assess toxicities and adverse events according to protocol 2. Grades, types or dates/duration of serious toxicities inaccurately recorded 3. Toxicities cannot be substantiated 4. Follow up procedures necessary to assess toxicities not performed 5. Failure to report toxicity and adverse events
Data quality:	<ol style="list-style-type: none"> 1. Recurrent missing source documentation to support data points on CRFs 2. Protocol specific laboratory or radiology tests not documented 3. Frequent and recurrent data inaccuracies 4. Frequent and recurrent errors in submitted data

14.11.4 Pharmacy Operations:

Accountability and storage of Study Agent:	<ol style="list-style-type: none"> 1. Study agent not stored separately by protocol 2. Study agents not stored under proper conditions 3. Study agent stored in insecure dispensing area 4. Inability to track receipt, use and disposition of study agent per protocol 5. Study agent transferred between sites with adherence to TN transfer policies 6. Study agent used for non-registered subjects 7. Multiple drug accountability records incomplete and/or not kept up on timely basis 8. Drug accountability records routinely filled out incorrectly (e.g. Incorrect agent, dose, route of administration, or dates documented)
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14.12 Final Audit Categories

Acceptable	<ol style="list-style-type: none"> 1. No deficiencies identified 2. Few lesser deficiencies identified 3. Major deficiencies identified that were addressed and/or corrected PRIOR to the audit completion
Acceptable, Needs Follow-Up	<ol style="list-style-type: none"> 1. Multiple lesser deficiencies identified 2. Major deficiencies identified during the audit not corrected and/or addressed prior to audit completion
Unacceptable	<ol style="list-style-type: none"> 1. Multiple major deficiencies identified 2. Single flagrant major deficiency identified 3. Multiple lesser deficiencies of a recurring nature found in a majority of the subject cases reviewed

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

14.13 **Special Audits**

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

14.14 **Audit Reports**

During the audit, forms to document those present at the audit and details of the studies and cases reviewed will be completed and retained in the TrialNet site's file. Any problems or concerns regarding compliance or data validity, accuracy or completeness will be noted. Any suspicion of scientific misconduct will be reported immediately to the NIH.

- a. Preliminary Report of Audit Findings:
This form documents major deficiencies in regulatory, pharmacy or subject cases. It will be e-mailed to the NIH and the Clinical Monitoring Group within 24 hours of leaving the audit site if major deficiencies are found at the site. This report will be copied to the Site Principal Investigator, the Site Study Coordinator and the TNCC Principal Investigator.
- b. Report of Audit Findings:
A narrative summary letter outlining the findings of the audit will briefly summarize overall findings of IRB approval, informed consent content, study agent handling and accountability and contents and accuracy of subject records. Deficiencies found during the audit will be discussed and a description of any corrective plans will be noted. The exit interview will be summarized. The audit

team's overall assessment of the audit and recommendations for the next audit will be included with the notation that it is pending NIH and Clinical Monitoring Group review. This report is due within 10 working days of the audit to the TrialNet site Principal Investigator. This report will also be sent to the NIH, the Clinical Monitoring Group, the Study Chair, the TNCC Principal Investigator and the Site Study Coordinator.

c. Final Report of Audit Findings:

A narrative summary letter outlining the findings of the audit will briefly summarize overall findings of IRB approval, informed consent content, study agent handling and accountability and contents and accuracy of subject records. Deficiencies found during the audit and any corrective action will be discussed and a description of any further corrective plans will be noted. The exit interview will be summarized. Audit team assessment and recommendations for the next audit interval will be reported. A copy of any responses by the TrialNet site Principal Investigator will be included in the Final Report. This will be completed and sent to the TrialNet site Principal Investigator within 12 weeks of the audit. A copy of the final report will also be sent to the NIH, the Clinical Monitoring Group, the Study Chair, the TNCC Principal Investigator and the Site Study Coordinator.

References:

NIH NCI-CTMB Guidelines for monitoring of clinical trials for cooperative group, as posted online

Required Study Documentation: E6 GCP ICH 8.2

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

Study agent records [21 CFR 312.57(c)] [21 CFR 312.62(c)]

Requirements for Expedited IRB approval (45 CFR 46.110)

Subject recruitment and advertising documentation (21 CFR 50.20, 50.25, 56.111(a)(3) and 812.20(b)(11))

Informed Consent Requirements: 21 CFR 50.25 and 45 CFR 46.116

15. APPENDICES

[Appendix B. Preparation for a MMTT](#)

[Appendix C. Urinalysis Test Instructions](#)

[Appendix D. MMTT Instructions](#)

[Appendix E. Tanner Stages](#)

[Appendix F. Concomitant Medications Log Instructions](#)

[Appendix G. Protocol Deviation Checklist](#)

[Appendix H. Reimbursement](#)

[Appendix I. Summary of Visit Windows](#)

[Appendix J. Study Prescription Form](#)