Protocol TN14
Effects of Canakinumab On The Progression of Type 1 Diabetes In New Onset Subjects

Antoinette Moran, MD

Manual of Operations
Version 2.0 10JAN2011

MANUAL OF OPERATIONS

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1 INTRODUCTION

1.1 Document Description

This Manual of Operations (MOO) has been created to provide details concerning the design, conduct, performance, monitoring, recording, analysis, and reporting of the study to assure that the data and reporting results are accurate and that the rights, integrity, and confidentiality of the participants are protected.

Guideline: A Manual of Operations (MOO) is required for each TrialNet study.

Principles:

- The MOO will be a cooperative work between the Study Chair, Network and the TNCC, with the Study Chair/designee holding responsibility to document proper screening, eligibility determination, and study visit procedures.
- The TNCC will author sections about technical systems and data collection processes.
- The MOO is a fluid document; it can be edited and updated throughout the life of the protocol.
- The TNCC will hold the “master” MOO document, and will post only the latest versions to the TrialNet Web site.
- The MOO must be approved by both the Study Chair/Designee and the TNCC before study initiation.

Process:

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

1.2 Current Protocol Synopsis (11AUG10)

Title	Effects of Canakinumab On The Progression of Type 1 Diabetes In New Onset Subjects
IND Sponsor	Type 1 Diabetes Trial Network (TrialNet)
Conducted By	Type 1 Diabetes Trial Network (TrialNet)
Protocol Chair	Antoinette Moran, MD
Accrual Objective	66 subjects over 2 years
Study Design	The study is a two-group, multicenter, randomized, double-masked, placebo-controlled Phase II clinical trial. All groups will receive standard intensive diabetes treatment with insulin and dietary management. 66 subjects will be randomly assigned to receive either monthly subcutaneous injections of 2.0 mg/kg canakinumab, or placebo for 12 months.
Treatment Description	Canakinumab is a fully human anti-interleukin-1β (anti-IL-1β) monoclonal antibody (IgG-1κ class). Canakinumab is designed to bind to human IL-1β and to functionally neutralize the bioactivity of this pro-inflammatory cytokine. Participants randomly assigned to canakinumab treatment or placebo will receive a total of 12 injections over one year.
Study Duration	All subjects will be followed for 1 year of treatment plus 1-3 years of additional follow-up until study end. Enrollment is expected to occur over two years.
Objective	To assess the safety, efficacy, and mode of action of canakinumab injections for the treatment of individuals with new onset type 1 diabetes.
Primary Outcome	The primary statistical hypothesis to be assessed in this study is whether the mean C-peptide response to MMTT at one year for subjects in the canakinumab treatment group will differ significantly from the mean value for placebo treated subjects.
Secondary Goals	The study will also examine the effect of the proposed treatments on surrogate markers for immunologic effects, namely disease-specific metabolic and immunologic outcomes
Major Inclusion Criteria	Type 1 diabetes within the past 3 months. Age 6-45 years. At least one diabetes associated autoantibody.

1.3 Participating Sites and Study Contacts

TN14 Anti IL-1Beta Study Participating Sites			
Participating Site Name & Address	**Site Number**	**Study Contact Person(s)**	**Telephone # & Email Address**
University of Florida Gainesville, FL 32610-0296	01	Site PI: Desmond Schatz, MD	Ph.: (352) 334-0857 Fax: (352) 392-4956 Email: schatda@peds.ufl.edu
		Site Trial Coordinator: Roberta Cook	Ph.: (352) 334-0857 Fax: (352) 334-3865 Email: cookrb@peds.ufl.edu
Yale School of Medicine New Haven, CT 06520-8089	02	Site PI: Kevan Herold, MD	Ph.: (203) 785-5637 Fax: (203) 737-5637 Email: kevan.herold@yale.edu
		Site Trial Coordinator: Laurie Feldman	Ph.: (203) 737-2760 Fax: (203) 785-7450 Email: laurie.feldman@yale.edu
Stanford University Stanford, CA 94305	05	Site PI: Darrell Wilson, MD	Ph.: (650) 723-5791 Fax: (650) 725-8375 Email: Dwilson@stanford.edu
		Site Trial Coordinator: Trudy Esrey	Ph.: (650) 498-4450 Fax: (650) 725-5837 Email: tesrey@stanford.edu
University of Miami Miami, FL 33136	06	Site PI: Jennifer Marks, MD	Ph.: (305) 243-6433 Fax: (305) 243-3313 Email: jmarks@miami.edu
		Site Trial Coordinator: Della Matheson	Ph.: (305) 243-3781 Fax: (305) 243-3313 Email: dmatheso@med.miami.edu
Barbara Davis Center of Childhood Diabetes Aurora, CO 80045	07	Site PI: Peter Gottlieb, MD	Ph.: (303) 724-6714 Email: Peter.Gottlieb@ucdenver.edu
		Site Trial Coordinator: Whitney Kastelic	Ph.: (303) 724-7502 Fax: (303) 724-6707 Email: whitney.kastelic@ucdenver.edu
University of Minnesota Minneapolis, MN 55455	**09**	**Study Chair/Site PI: Toni Moran, MD**	**Ph: (612) 624-5409 Fax: (612) 626-5262 Email: moran001@umn.edu**
		Site Trial Coordinator /TCC: Jennifer Smith	**Ph.: (612) 624-6682 Fax: (612) 644-5206 Email: smit5759@umn.edu**
Benaroya Research Institute Seattle, WA 982101	10	Site PI: Carla Greenbaum, MD	Ph. Main: (206) 515-5232 (ass't Marilyn Reeve) Ph. Second #: (206) 515-5231 Fax: (206) 515-5239 Email: cjgreen@benaroyaresearch.org mreeve@benaroyaresearch.org
		Site Trial Coordinator: Heather Vendettuoli	Ph.: (206) 341-1928 Fax: (206) 515-5239 Email: HVendettuoli@benaroyaresearch.org

University of California – San Francisco San Francisco, CA 94143	11	Site PI: Stephen Gitelman, MD	Ph.: (415) 476-3748 Fax: (415) 476-8214 Email: sgitelma@peds.ucsf.edu
		Site Trial Coordinator: Celia Hamilton	Ph.: (415) 476-5026 Fax: (415) 476-8214 Email: HamiltonC@peds.ucsf.edu
University of Texas Dallas, TX 75390-9072	12	Site PI: Philip Raskin, MD	Ph.: (214) 648-2017 Fax: (214) 648-4854 Email: philip.raskin@utsouthwestern.edu
		Site Trial Coordinator: Renee Davis	Ph.: (214) 648-4830 Fax: (214) 648-3816 Email: Renee.Davis@UTSouthwestern.edu
The Hospital for Sick Children Toronto, ON Canada, MSG-1X8	13	Site PI: Diane Wherrett, MD	Ph.: (416) 813-8159 Fax: (416) 813-6304 Email: diane.wherrett@sickkids.ca
		Site Trial Coordinator: Lesley Eisel	Ph.: (416) 813-7654 x1798 Fax: (416) 813-2252 Email: lesley.eisel@sickkids.ca
University of Pittsburgh Pittsburgh, PA 15201	14	Site PI: Dorothy Becker, MD	Ph.: (412) 692-5179 Fax: (412) 692-5834 Email: dorothy.becker@chp.edu
		Site Trial Coordinator: Karen Riley	Ph.: (412) 692-5210 Fax: (412) 692-6449 Email: karen.riley@chp.edu
Columbia University New York, NY 10032	15	Site PI: Robin S. Goland, MD	Ph: (212) 851-5492 Fax: (212) 851-5460 Email: rsg2@columbia.edu
		Site Trial Coordinator: Ellen Greenberg	Ph.: (212) 851-5425 Fax: (212) 851-5460 Email: emg25@columbia.edu
Indiana University- Riley Hospital for Children Indianapolis, IN 46202	16	Site PI: Mark Pescovitz, MD	Ph.: (317) 274-1010 Fax: (317) 278-0264 Email: mpescov@iupui.edu
		Site Trial Coordinator: Jennifer Terrell	Ph.: (317) 944-2574 Fax: (317) 944-2579 Email: jkramey@iupui.edu
Vanderbilt University	3126	Site PI: William Russell, MD	Ph.: (615) 936-TNET Fax: (615) 936-7001 Email: bill.russell@vanderbilt.edu
		Site Trial Coordinator: Anne Brown	Ph.: (615) 343-5968 Fax: (615) 936-7001 Email: anne.brown@vanderbilt.edu

TN14 Anti IL-1Beta Study TrialNet Coordinating Center (TNCC)		
USF TrialNet Coordinating Center (TNCC) University of South Florida Pediatrics Epidemiology Center Tampa, FL 33615	Primary Contact: AQesha ”Q” Ritzie	Ph.: (813) 396-2681 Fax: (813) 910-5994 Email: aqesha.ritzie@epi.usf.edu
	Secondary Contact: Joy Ramiro	Ph.: (813) 396-9211 Fax: (813) 910-5976 Email: Joy.Ramiro@epi.usf.edu

TN14 Anti IL-1Beta Study CENTRAL PHARMACY		
EMINENT Services Corporation 7495 New Technology Way Frederick, MD 21703-9401	Raghuveera ”Raghu” Yaramolu	Ph.: (240) 629-1972 Ext 107 Fax: (240) 629-3298 Email: ryaramolu@emiserv.com

TN14 Anti IL-1Beta Core Laboratory Contact Information			
Specimens	**Lab Address Information**	**Contact for results**	**Phone and Email Address**
Chemistries, MMTT HbA1c, HIV, Hep B, Hep C	Specimen Processing Core B-Cell Function/Biochemistry Laboratory Northwest Lipid Research Laboratories University of Washington 401 Queen Anne Avenue North Seattle, WA 98109	Jessica Chmielewski	Ph.: (206) 543-3694 Email: jjc8@u.washinton.edu
Flu and Tetanus Serology	Viral Research Lab University of Colorado Denver Pediatric Infectious Disease 12700 E. 19th Avenue Core Viral Research Laboratory 2, Lab11480 Aurora, CO 80045	N/A	Kelly – Ph.: (303) 724-4483 Julie – Ph.: (303) 724-4481 Jennifer - Ph.: (303) 724-4484 Email: Kelly.Richardson@ucdenver.edu Julie.Patterson@ucdenver.edu Jennifer.Canniff@ucdenver.edu
HLA DNA	Attn: HLA/DNA LAB Barbara Davis Center 1775 Aurora Court, UC Denver, AMC M20-4201E Aurora, CO 80045	Taylor Armstrong or Sunanda Babu	Ph.: (303) 724-6809 Email: Taylor.Armstrong@ucdenver.edu Sunanda.Babu@ucdenver.edu
NIDDK: Cytokine Immunogenicity Mechanistic Serum PBMC/Plasma PK/Cytokine	NIDDK Biosample Repository Fisher BioServices 20301 Century Blvd., Bldg. 6, Suite 400 Germantown, MD 20874	N/A	Ph.: (240) 686-4703
RNA Processing Core Laboratory	The TrialNet RNA Lab Jinfiniti Biosciences Center of Innovation for Life Sciences Medical College of Georgia 1120 15th Street, CA 2105 Augusta, GA 30912-7624	N/A	(706) 721-9461 receiving@jinfiniti.com
Viral Serology: CMV IgG and IgM; EBV IgG and IgM EBVPCR; CMVPCR	Viral Clinical Lab University of Colorado Hospital 12401 E. 17th Avenue Clinical Lab-LOB Room 253 Aurora, CO 80045	Kathi Wilcox	Ph.: (720) 848-7031 Email: Kathi.Wilcox@uch.edu

2 STUDY PERSONNEL RESPONSIBILITIES

2.1 Principal Investigator (Site PI)

The site PIs are responsible for supervising that 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 SOPs (standard operating procedures) at the site to ensure that the study is conducted and data generated, documented, and reported in compliance with the protocol, GCP, and the 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. Ensuring that all site investigators and research staff are fully aware of their obligations.
4. Ensuring local site initial and continuing Institutional Review Board (IRB) review and approval of the protocol (amendments, changes, updates, etc).
5. Reviewing local site adverse events (AEs) and ensuring that AEs have been addressed appropriately and reported correctly.
6. Supervising the preparation of training materials and procedure manuals at the site.
7. Reviewing all trial and patient care issues that occur at the local site.
8. Monitoring protocol compliance at the local site and advising 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. Screen participants and participate in enrollment and the consent process.
2. Coordinate participant's visits to the clinical center.
3. Utilize and maintain source documents in accordance with the Code of Federal Regulations and the ICH Guidelines for Good Clinical Practice (GCP)
4. Enter data into electronic case report forms (e-CRFs).
5. Order study supplies.
6. Respond to data queries / requests for information by the TNCC or Study Chair
7. Assist in preparation of the IRB submission and writing study documents.
8. Additional duties as delegated per the site delegation log

2.3 Role of the TrialNet Coordinating Center

The TrialNet Coordinator Center (TNCC) was established as part of the TrialNet Network to support the data management and analysis of research data for the network and to identify opportunities to implement data standards and share resources across the network. The TNCC participates in the design of clinical protocols, management of the protocol, and amendment approval process, in addition to providing the data management and analysis necessary to support them. They facilitate data entry by building and maintaining data entry forms. The TNCC has developed and maintains the "Protocol Manager" clinical data management system used for the collection, storage, and analysis of data for all clinical sites that participate in network studies. They are also responsible for generation of reports and analyzing data for this study in conjunction with the PI and his/her program coordinator.

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

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

3 STEPS TO SITE ACTIVATION

Enrollment cannot begin until the Site Initiation Process has been completed and TNCC has cleared the study site for enrollment (See Appendix C for Site Activation Checklist).

Steps to site activation are as follows:

1. The site must submit to the TNCC an appropriate **IRB approval** for the study to be activated (as detailed below, section 3.1)
2. The site must submit to the TNCC an up-to-date **site delegation log** reflecting the current study and detailing the responsibilities of each staff member as designated by the site PI (as detailed below, section 3.2)
3. The site must submit to the TNCC the appropriate **Duality of Interest form(s)** for each individual listed on the site delegation log (as detailed below, section 3.3)
4. At least **one person at the site must be trained** on the online data capture system (protocol manager) and be certified for all required study procedures and tests (as detailed below, section 3.4)

3.1 IRB Approval

→ Definition: Appropriate IRB approval- Correspondence from the IRB of record for the study site indicating that the TrialNet protocol (and related materials) were approved.

→ Requirements for IRB approval

1. An actual letter or correspondence indicating that the project was/is approved (with reference to the correct TrialNet protocol title)
2. The date of the approval letter/correspondence
3. IRB Chair (or chair designee) signature
4. Explicit reference to what the IRB 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 approval/correspondence pertains
5. If applicable, IRB approved informed consent(s)/assent(s) indicating the valid from and valid through dates (one year or date of current approval until time of continuing review renewal). Consents should be stamped or IRB policy should be provided describing quality control/document version control procedures.

3.2 Site Delegation Log

→ Definition: Site Delegation Log- A comprehensive list, current and maintained at each study site, detailing the name, credentials, time began service on a protocol, time ended service on a protocol, explicit description of protocol responsibilities for each site staff member directly involved in the conduct of the research (e.g., study coordinator, sub-Investigator) or staff associated with, but not directly involved in, the research trial (e.g., pharmacist, laboratory staff).

→ Requirements of the Site Delegation Log:

1. All TrialNet sites are required to have a site delegation log reflecting each study in which the site participates
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 study site Principal Investigator.
3. The log must contain the signature of the site Principal Investigator

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 and must be retained with other study-related documents in accordance with applicable regulations.

→ 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 persons' 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

The current SDL is available online in the Sites – Documents for Download → Current Site Forms folder

3.3 Duality of Interest forms

Each person listed on the site delegation log must have a duality of interest on file with the TNCC and it must be updated at each steering committee meeting. The duality of interest forms can only be completed online (see below step by step process on how to access the online form). A list of the required forms will be emailed to a site prior to study activation if the site requests the forms or if- for all individuals on the site delegation log- an online form has not yet been completed.

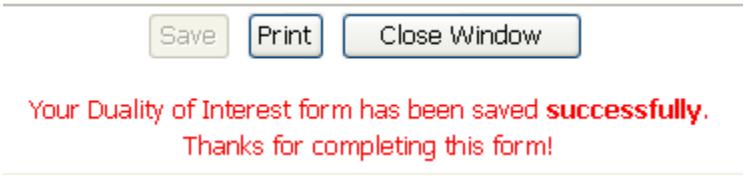
To access the online form:

Step 1. From the main web site, on the left side navigation bar, click on the link "Duality Disclosure Form"

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

Step 3. Read and complete the form. It is important to pay special attention to section 11-dualities or revisions by protocol.

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



Step 5. Hit the “close window” button

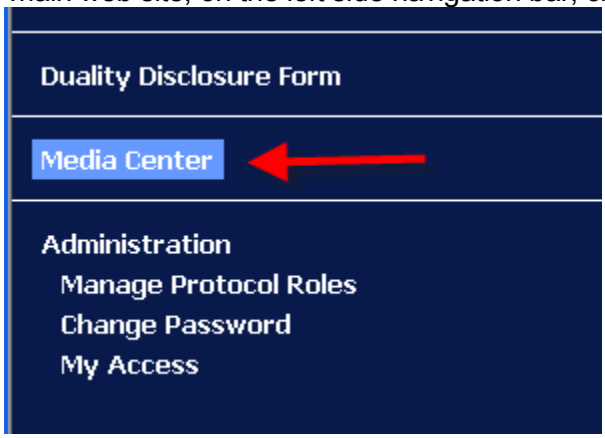
3.4 Study/System Training

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

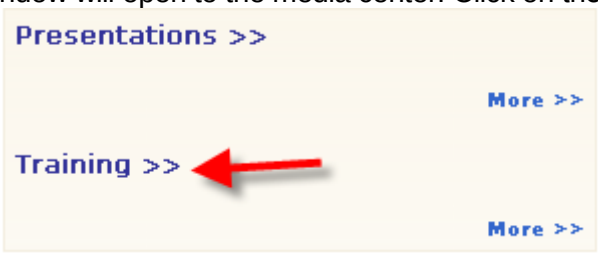
3.4.1 Online Training

Demonstration and training videos are available online. **You must have windows media player** in order see the videos; they can be viewed at any time by navigating to the online media center as follows:

Step 1. From the main web site, on the left side navigation bar, click on the link “Media Center”



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



Step 3. Select the protocol/session on/of which you’d like to view the training
Protocol Training – TN14 Anti IL-1Beta (Canakinumab)

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

EXAMPLE SNAPSHOT of TN08:

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

Title	Speaker	Date
Neurologic Assessment	NIH	3/6/2009
TN08 Pharmacy Training	Kate Paulus	3/25/2009
TN08 Online Protocol Tools	Joy Ramiro	3/25/2009
TN08 Online Forms By Visit	Heather Guillette	3/25/2009
TN08 Online Participant Registration	Heather Guillette	3/25/2009
TN08 Online Treatment Assignment and Randomization	Heather Guillette	3/25/2009
GENERAL Adverse Event Reporting	Heather Guillette	3/25/2009
GENERAL Members Directory Overview	Heather Guillette	3/25/2009
GENERAL Members Website Overview	Heather Guillette	3/25/2009
GENERAL Protocol Manager Overview	Heather Guillette	3/25/2009
TN08 Specimen Collection and Shipment Procedures	Joy Ramiro	3/25/2009
TN08 Protocol Overview	Diane Wherrett M.D.	3/27/2009

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.

The training modules and descriptions of modules available are as follows:

1) TN14 Protocol Overview: Provides a description of the protocol, eligibility criteria, purpose, specific aims, and details of procedures
2) TN14 Pharmacy Overview: Provides an overview of pharmacy related procedures including drug ordering, dispensing, agent return, etc
3) TN14 Protocol Tools & Web Overview: Provides a description of tools available on the TNCC Protocol Manager page including protocol documents, checklists, reports, source documents, MOO, pharmacy manual, etc
4) TN14 Online Forms By Visit: Provides a brief overview of e-CRF(s) available for the study by visit
5) TN14 Online PRN Forms: Provides a brief overview of PRN e-CRF(s) available for the study
6) TN14 Online Participant Registration: Provides a guided tutorial of how to register a participant
7) TN14 Online Treatment Assignment and Randomization: Provides a guided tutorial of how to assign treatment to a participant
8) TN14 Specimen Collection and Shipment Procedures: Provides an overview of study test/assay collection and shipment procedures as well as supplies needed by test
9) GENERAL Adverse Event Reporting: Provides a non-study specific overview of how to use the online adverse events system
10) GENERAL Members Directory Overview: Provides a non-study specific overview of how to use the online member director
11) GENERAL Members Website Overview: Provides a non-study specific overview of how to use the online members website
12) GENERAL Protocol Manager Overview: Provides a non-study specific overview of how to use the online protocol manager page and related sections.

3.4.2 Canakinumab Certification Quiz

The Canakinumab Certification Quiz is available online and should be completed by all individuals listed in roles on the site delegation log requiring a knowledge of study procedures. Once the certification quiz has been completed it should be sent to the TNCC CRA for the study.

4 RECRUITMENT PROCEDURES AND STRATEGIES

4.1 Recruitment Strategy-General

The study involves geographically distributed clinical centers with a specific interest in Type 1- Diabetes as defined by inclusion and exclusion criteria (see below). They are likely to capture most of the available study population at their clinics. Participants will also be recruited by information posted on the TrialNet website, ClinicalTrials.gov and diabetes camps. Patients followed by the investigators in their clinics and patients who send their contact information to the investigators will be contacted by the investigators or their designated staff and invited to participate. Both newly diagnosed participants and participants recruited after diagnosis can participate. It is recognized that data collected prospectively from newly diagnosed patients may differ from that collected from patients with established diagnosis. Some of the differences may relate to disease duration and some may relate to interventions instituted following the diagnosis. Data regarding disease duration and treatments will be collected and will be used to adjust for differences between the two groups.

4.2 Recruitment Goals

66 subjects over 2 years
Activation date: TBD

4.3 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 (by the site) via the eligibility e-CRF.
    - If ineligible and participant did or did not complete the screening visit and you did not ask the participant all the eligibility questions please complete Pre-Randomization Exit form.
    - If ineligible and participant did complete the screening visit and you did ask the participant all the eligibility questions please complete 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
    - Study: by site, total number of subjects registered and- of those- total number randomized.
    - By site: total number of subjects 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

4.4 Eligibility Criteria

Inclusion Criteria:

The participant MUST:

1. Be 6 to 45 years of age at the time of randomization, this indicates that at the time of randomization the participant has passed his/her 6th 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:

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

Or

2. 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

3. 2-hour plasma glucose is ≥ 200 mg/dl (11.1 mmol/L) during a 75 gram oral glucose tolerance test (OGTT)

Or

4. 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
- If date of diagnosis is questionable, then the TrialNet principal investigator should contact the TN study chair and/or request the assistance of the eligibility/deviation committee and explain the circumstances

3. Must have at least one diabetes–related autoantibody present.
    a. Islet-cell autoantibodies (ICA or ICA-512)
    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 7 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).
        ii. Zinc Transporter autoantibody (ZnT8) – If the GAD65H and IA-2H are negative then ZnT8 will be run even if the mIAA is present.
4. 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

5. At least one month from last live immunization
6. If female with reproductive potential, be willing to avoid pregnancy and have a negative pregnancy test during the 12 months of treatment and for an additional 3 months (see the note in section 6.7 page 77 for further explanation). A urine pregnancy test will be conducted at Screening, Baseline, All visits except optional visit 6A. Acceptable forms of birth control include, but are not limited to:
    a. Abstinence
    b. Barrier methods (condom, diaphragm, cervical cap, sponge, or spermicide)
    c. Contraceptives (oral or implant)
    d. Surgical methods (sterilization or intrauterine devices)
    *Please note that female subjects with reproductive potential should be encouraged to use two forms of birth control. They will not be excluded from the study if they only use one acceptable form of birth control.
7. Must be willing to forgo live vaccinations during the 12 months of treatment and for an additional 3 months
8. Must be willing to comply with intensive diabetes management
9. Weigh at least 20 kg (44lb) at study entry. This is to ensure that the participant is of sufficient body weight to allow for the blood volumes drawn for the study assessments.

Exclusion Criteria:

The participant MUST NOT:

1. Be immunodeficient or have clinically significant chronic lymphopenia
2. Have an active infection
3. Have a positive purified protein derivative of tuberculin (PPD) test result. The PPD test is administered at the initial screening visit. A positive PPD indicates that the participant has been infected with Tuberculosis, and should be referred for appropriate counseling and treatment.
4. Be currently pregnant or lactating, or anticipate getting pregnant for 24 months after first injection. If the participant has any plans to become pregnant, or to attempt to become pregnant, during the course of the study she should be excluded from participation.
5. On-going use of medications known to influence glucose tolerance.
6. Currently using warfarin
7. Require use of other immunosuppressive agents. Such as chronic use of steroids, regardless of the type or route of administration (inhaled, topical, systemic, oral, etc.). Chronic use of steroids is defined as more than one-week of continuous use over the course of one-month. Acute use of steroids should not be considered grounds for exclusion, as long as the participant is not continuing to take the steroid medication at the time of screening.
8. Have serologic evidence of current or past HIV, Hepatitis B (surface antigen and core antibody), or Hepatitis C infection. Participants are screened for Human Immunodeficiency Virus (HIV), Hepatitis B virus, and Hepatitis C virus at the initial screening visit to determine if they are currently infected with these viruses. Note that if the participant is infected with HIV or Hepatitis, this information must be reported to the appropriate department of health.
9. Have any complicating medical issues or abnormal clinical laboratory results that interfere with study conduct or cause increased risk to include pre-existing cardiac disease, COPD, neurological, or blood count abnormalities (such as lymphopenia, leucopenia, or thrombocytopenia)
10. Have history of malignancies
11. Be currently using non-insulin pharmaceuticals to affect glycemic control. If a participant and their prescribing physician are willing to stop therapy with these agents then they will be eligible for study participation following a two week (14 day) washout period.
12. Be currently participating in another type 1 diabetes treatment study

4.5 Rationale for Inclusion and Exclusion Criteria

These criteria have been selected because of the lack of treatment options for patients with Type 1 Diabetes. The inclusion criteria reflect the parameters for the diagnosing of Type 1 Diabetes and the need for treatment. The exclusion criteria reflect the need for having laboratory values within a safe range before treatment would start.

4.6 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 and Events Committee will review and adjudicate the situation. See Appendix B for a copy of the form that needs to be completed and submitted to the TNCC for this review to take place.

5. VISIT PROCEDURES

Before any study specific procedures a copy of the Informed Consent, the Volunteer Understanding Assessment and the Participant Handbook will be given to the participant. Please refer to section 7 for a complete description of the Informed Consent Process for the study.

Definitions and instructions are available in section 6 for each type of procedure/ assessment/ test/ assay listed in this section.

5.1 Study Visit/Procedures Schedule and Windows

	Screening	Treatment Administration													1yr FU		2-4 yr FU				
Visit ->	**-1₃**	**1**	**2**	**3**	**4**	**5**	**6**	**6A**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Month ->	*-1*	*0*	*1*	*2*	*3*	*4*	*5*	*5+ 1week*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*18*	*24*	*30*	*36*	*42*	*48*
Year -->	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2	2	3	3	4
Procedure/Assessment																					
Medical History	X																				
Interim Medical History		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X			X				X			X			X	X	X	X	X	X	X
AE Assessment		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Participant/Parent Survey*					X										X		*	*	*	*	*
Concomitant Medication	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
PPD	X																				
Urine Pregnancy	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration		X	X	X	X	X	X		X	X	X	X	X	X							
Tetanus Immunization														X							
Flu vaccine				X_1 or after																	
Diabetes Management		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X

Final Participant/Parent Survey will be administered at the end of the trial prior to debriefing

	Screening	Treatment Administration													1yr FU		2-4 yr FU				
Visit ->	**-1_3**	**1**	**2**	**3**	**4**	**5**	**6**	**6A**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Month ->	*-1*	*0*	*1*	*2*	*3*	*4*	*5*	*5+ 1week*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*18*	*24*	*30*	*36*	*42*	*48*
Year -->	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2	2	3	3	4
ECRF(s)																					
Treatment Start Date		X																			
Screening ICF Verification	X																				
Demographics	X																				
Family History	X																				
Eligibility		X																			
Screening Medical History	X																				
Interim Medical History		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Physical Exam	X	X			X				X			X			X	X	X	X	X	X	X
Pregnancy Monitoring only (if applicable)		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Participant/Parent Survey (TELEFORM)*see pg 20*					X										X						
Concomitant Medication	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration		X	X	X	X	X	X		X	X	X	X	X	X							
Diabetes Management		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Optional Visit 6A (If applicable)								X (PRN)													
CBC w/ Differential Results	X								X						X						
SPECIMEN COLLECTION e-FORM																					
Chemistries	X								X						X						
HIV/HEPB/HEPC	X																				
Autoantibodies	X																				
EBV/CMV Viral Serology	X																				
EBV – Viral Load EBVPCR	X																				
EBV – Viral Load EBV PCR (EBV Seronegative Only)		X	X	X	X	X	X		X	X	X	X	X	X	X		X				

	Screening	Treatment Administration													1yr FU		2-4 yr FU				
Visit ->	**-1_3**	**1**	**2**	**3**	**4**	**5**	**6**	**6A**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Month ->	*-1*	*0*	*1*	*2*	*3*	*4*	*5*	*5+ 1week*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*18*	*24*	*30*	*36*	*42*	*48*
Year -->	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2	2	3	3	4
ECRF(s) ~continued~																					
HbA1c		X			X				X			X			X	X	X	X	X	X	X
Flu vaccine (PRN)				X_1 or after																	
Tetanus Vaccination														X							
SPECIMEN COLLECTION e-FORM																					
Flu serology				X_1 or after	X_2																
Tetanus Serology														pre	post						
4hr MMTT	X								X						X		X				
2hr MMTT ≥12			X		X			X (PRN)				X				X		X	X	X	X
2hr MMTT < 12	X		X		X			X (PRN)	X			X			X	X	X	X	X	X	X
Serum - PK/Cytokine (pre-dose)		X	X	X	X		X														
Serum - PK/Cytokine (1 hr post-dose)		X	X	X																	
Serum - PK/Cytokine (anytime)															X	X					
SPECIMEN COLLECTION e-FORM: MECHANISTIC STUDIES																					
Whole Blood - HLA		X																			
Mechanistic Serum	X	X			X		X		X			X			X	X	X	X	X	X	X
Serum - Cytokines		X			X		X		X			X			X	X	X	X	X	X	X
Serum - Immunogenicity		X			X		X		X			X			X	X	X	X	X	X	X
Whole Blood - Plasma/PBMC	X	X							X						X		X				
Whole Blood - RNA		X			X				X						X		X				

	Screening	Treatment Administration													1yr FU		2-4 yr FU				
Visit ->	**-1_3**	**1**	**2**	**3**	**4**	**5**	**6**	**6A**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Month ->	*-1*	*0*	*1*	*2*	*3*	*4*	*5*	*5+ 1week*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*18*	*24*	*30*	*36*	*42*	*48*
Year -->	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2	2	3	3	4
SAMPLES DRAWN																					
CBC w/ Differential Results	X								X						X						
Chemistries	X								X						X						
HIV/HEPB/HEPC	X																				
Autoantibodies	X																				
EBV/CMV Viral Serology	X																				
EBV – Viral Load EBV PCR	X																				
EBV – Viral Load EBV PCR (EBV Seronegative Only)		X	X	X	X	X	X		X	X	X	X	X	X	X		X				
Flu serology				X_1 or after	X_2																
Tetanus Serology														pre	post						
HbA1c		X			X				X			X			X	X	X	X	X	X	X
4hr MMTT	X_3														X		X				
2hr MMTT ≥12			X		X			X (PRN)	X			X				X		X	X	X	X
2hr MMTT < 12	X_3		X		X			X (PRN)	X			X			X	X	X	X	X	X	X
Serum - PK/Cytokine (pre-dose)		X	X	X	X		X														
Serum - PK/Cytokine (1hr post-dose)		X	X	X																	
Serum - PK/Cytokine (anytime)															X	X					
MECHANISTIC STUDIES																					
Whole Blood – HLA		X																			
Mechanistic Serum	X	X			X		X		X			X			X	X	X	X	X	X	X
Serum - Cytokines		X			X		X		X			X			X	X	X	X	X	X	X
Serum - Immunogenicity		X			X		X		X			X			X	X	X	X	X	X	X

	Screening	Treatment Administration													1yr FU		2-4 yr FU				
Visit ->	**-1[3]**	**1**	**2**	**3**	**4**	**5**	**6**	**6A**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Month ->	*-1*	*0*	*1*	*2*	*3*	*4*	*5*	*5+ 1week*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*18*	*24*	*30*	*36*	*42*	*48*
Year -->	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2	2	3	3	4
MECHANISTIC STUDIES	**SAMPLES DRAWN ~continued~**																				
Whole Blood - Plasma/PBMC	X	X							X						X		X				
Whole Blood - RNA		X			X				X						X		X				

VISIT WINDOWS

	Screening	Treatment Administration													1yr FU		2-4 yr FU				
Visit ->	**-1[3]**	**1**	**2**	**3**	**4**	**5**	**6**	**6A**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Month ->	-1	0	1	2	3	4	5	*5+ 1week*	6	7	8	9	10	11	12	18	24	30	36	42	48
Year -->	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2	2	3	3	4
Visit Windows																					
		X[7]	X[4]	X[4]	X[4]	X[4]	X[4]	X[5]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]

Footnotes:

1 Estimated study visit for administering annual kill flu vaccine. Seasonal Flu Vaccine will be provided by TrialNet up to and including visit 12 only.

2 Blood draw assessing immune response next visit after killed flu vaccine administration.

3 Screening Visit: Screening MMTT must be at least 3 weeks after diagnosis and within one month (37 days) of randomization (if greater than 37 days of randomization – repeat MMTT)

4 +/- 7 days

5 1 week from the date of visit 6 with a window +/- 2 days

6 +/- 14 days

7 Baseline visit must occur no more than 100 days from date of diagnosis

5.2 Visit -1 (Screening): For ECRF Screen Shots go to section 9.0

Prior to the screening visit, the site coordinator should do the following:

Step 1. Schedule the participant for the screening visit. **Remind the participant that they need to be fasting for this visit.**

Step 2. Order any supplies needed for the screening visit through the online Fisher supply ordering system. See section 6.4 for:

a. A list of supplies required by test assay
b. Lab procedures
c. Shipping procedures (if applicable)
d. Extended storage procedures (if applicable)

Step 3. Review visit checklist and ensure site is prepared for visit (procedures, etc). The checklists are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms"

At the screening visit, the site coordinator should do the following:

Step 1. Determine whether the subject is interested in the study; if so, proceed to step #2

Step 2. Administer the screening consent (and screening assent if subject is under the age of 18), local HIV screening consent (if applicable) and local HIPAA form (if applicable). If the subject signs all the applicable consent forms and decides to proceed with the study, continue to step #3

Step 3. Administer the volunteer survey (volunteer survey can be administered at either screening OR baseline visit) to ensure the subject understands the study and their responsibilities. The volunteer survey is located online in the TN14 Protocol Area, folder entitled "TN14 – (A) Documents for IRB Submission". **Make sure to go over any questions that the subject answers incorrectly and document this in your source documentation. ****Please note there is an assessment tool titled "Volunteer Understanding Assessment Review" located online in the TN14 Protocol Area, folder entitled "*TN14 – (C): Forms"

Step 4. Register the participant to the online system

Step 5. Clinical Assessments- use source documents to collect information for each of the clinical assessments. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms"

a. Collect subject's medical history
b. Ask the subject about what medications he/she is currently taking. **Please be sure to review the list of CYP450 contraindicated medications in section 13. If the subject is concurrently on any of the medications listed the PI should decide if any of these meds require frequent and close monitoring and discuss with subject and subject's treating physician.**
c. Conduct a physical exam

Step 6. Tests and Assays- **follow instructions in section 6.4 of this document for collection of specimens and shipment (use table of contents to jump to section)**

a. Conduct a PPD
b. Conduct a Urine Pregnancy Test for female participants with reproductive potential
    i. *Please note that female subjects with reproductive potential should be encouraged to use two forms of birth control. They will not be excluded from the study if they only use one acceptable form of birth control.
c. Conduct a 4-hour MMTT (or 2-hour MMTT if < 12 years old at time of screening) *refer to section 6.4.3 and appendix A for details*

d. Collect blood for:
   i. CBC with differential
   ii. Chemistries
   iii. Viral Serology – EBV, CMV, HIV, Hep B and C
   iv. EBV Viral Load – EBV PCR *(refer to section 6.2.5 for details)*
   v. Serum for Diabetes Autoantibodies
   vi. Mechanistic Assessments-
      1. Mechanistic Serum (*Please note that all TNCC mechanistic samples **except HLA** will get shipped to the NIDDK Repository for storage, please refer to section 6.4 for additional instructions)*
      2. Whole blood – Plasma/PBMC

Step 7. Remind subject to bring blood glucose and insulin records to next visit

Step 8. Enter data collected on source documents into the e-CRF(s) online. **Please note you must complete the Demographics e-CRF** in order for the MMTT form to populate.
   a. For participants < 12 a 2 hour MMTT will be conducted
   b. For participants ≥ 12 a 4 hour MMTT will be conducted

Step 9. Scan barcodes for each test/assay into the online specimen collection form(s)

Step 10. Ship specimens to lab(s) using the online shipment system- follow instructions in section 6.4 of this document for packaging and shipment of specimens. ***** IMPORTANT: PLEASE SHIP ALL SCREENING SAMPLES AS PRIORITY.**

Step 11. Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.

****NOTE PER SERUM FOR DIABETES AUTOANTIBODIES:**

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. The following procedure must be followed:

1. Contact participant and schedule re-draw. The scheduling of the re-draw, and time required for results to be reported, **must** fit within the eligibility window for the study (randomization must occur no more than 100-days from date of diagnosis and no more than 37 days from screening MMTT). Inform the TNCC of the redraw date for Autoantibodies so that the protocol CRA can be on the lookout for the results.
2. Complete a **new** specimen collection (PRN) form in the "Additional Study Forms/Events".

****NOTE PER MMTT:**

The mixed meal tolerance test (MMTT) will be conducted at least 3 weeks (21 days) from diagnosis of diabetes and within one month (37 days) of randomization. If the MMTT was conducted on a date which is greater than 37 days from randomization, the MMTT test will need to be repeated within the eligibility window for the study (randomization must occur no more than 100-days from date of diagnosis).

1. Contact participant and schedule another MMTT. The scheduling of the MMTT, and time required for results to be reported, **must** fit within the eligibility windows for the study (randomization must occur no more than 100-days from date of diagnosis). Inform the TNCC of the 2nd MMTT so that the protocol CRA can be on the lookout for the results.
2. Complete a **new** specimen collection (PRN) form in the "Additional Study Forms/Events".

5.3 Visit 1 Month 0 (Baseline):

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

Prior to the baseline visit, the site coordinator should do the following:

Step 1. Review the participant's eligibility; verify that subject meets all eligibility criteria for this study.

Step 2. Complete the online Eligibility e-CRF(You must complete the online Eligibility e-CRF to randomize a participant)
   a. If ineligible and participant did or did not complete the screening visit and you did not ask the participant all the eligibility questions please complete Pre-Randomization Exit form.
   b. If ineligible and participant did complete the screening visit and you did ask the participant all the eligibility questions please complete the Eligibility e-CRF.

Step 3. Randomize the participant in the online system; make note of the randomization number assigned to the participant.

Step 4. When ordering study drug
   a. For the **first** participant: Contact the TNCC no less than 1-week prior to the baseline visit date and notify the TNCC that a subject is scheduled for a baseline visit and that initial study drug is needed
   b. For **all subsequent** participants: follow procedures outlined in the Pharmacy Manual for the ordering of study drug

Step 5. Schedule the participant for the baseline visit.

Step 6. Notify site pharmacy of baseline visit (date) and inform pharmacy of randomization number for the participant.

Step 7. Order any supplies needed for the baseline visit through the online Supply Ordering system. See section 6.4 for a list of supplies required by test/assay

Step 8. Review visit checklist and ensure site is prepared for visit (procedures, etc). The checklists are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms"

At the baseline visit, the site coordinator should do the following:

Step 1. Ask the participant if he/she has any questions or concerns.

Step 2. Double-check participant's eligibility; verify that subject meets all eligibility criteria for this study.

Step 3. If not done at the screening visit, administer the volunteer survey to ensure the subject understands the study and their responsibilities. The volunteer survey is located online in the TN14 Protocol Area, folder entitled "TN14 – (A) Documents for IRB Submission". ***Please note there is an assessment tool titled "Volunteer Understanding Assessment Review" located online in the TN14 Protocol Area, folder entitled "***TN14 – (C): Forms"

Step 4. Administer the intervention consent (and intervention assent if subject is under the age of 18), and local HIPAA form (if applicable). If the subject (or parent/guardian) signs all the applicable consent forms and decides to proceed with the study, continue to step 5

Step 5. Clinical Assessments- use source documents to collect information for each of the clinical assessments. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms"
   a. Collect subject's medical history (any changes since last visit)

b. Ask the subject about his/her concomitant medications (changes since last visit)
c. Conduct a physical exam
d. Obtain information about Diabetes Management
e. Ask the participant if they have experienced any adverse events

Step 6. Tests and Assays- follow instructions in section 6.4 of this document for collection of specimens
a. Conduct a Urine Pregnancy Test if participant is female of childbearing potential
b. Collect blood for:
i. EBV Viral Load (EBV/PCR) – for participants Seronegative at screening ONLY
ii. HbA1c
iii. Serum – PK/Cytokine **pre** and **post** injection samples
iv. Mechanistic Assessments-
1. Whole Blood - HLA
2. Mechanistic Serum
3. Serum – Cytokines
4. Serum – Immunogenicity
5. Whole Blood – Plasma/PBMC
6. Whole Blood – RNA

Step 7. Protocol-Specific Activities: administer **first** dose of study agent. See section 6.2.2 for details. Use source documents to collect information for the administration of study drug. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”. *Please remember to collect the PK/Cytokine post dose sample **1 hour** post injection.* ***Note: this PK sample is the second PK blood draw for this visit. The first PK blood draw should be done before the injection of study drug.***

Step 8. Subject should remain at study site for observation for at least 1 hour following study drug administration

Step 9. Enter data collected on source documents into the e-CRF(s) online.

Step 10. Scan barcodes for each test/assay into the online specimen collection form(s)

Step 11. Ship specimens to lab(s) using the online shipment system- follow instructions in section 6.4 of this document for packaging and shipment of specimens.

Step 12. Retain all informed consent documents, materials from visit, and source documents in an organized fashion in a secured, double-locked room.

5.4 Visit 2 Month 1 (Baseline + 1month):

Window: +/- 7 days

Prior to visit, the site coordinator should do the following:

Step 1. Schedule the participant for the visit. **Remind the participant that they need to be fasting for this visit.**

Step 2. Order any supplies needed for the visit through the online Fisher supply ordering system. See section 6.4 for a list of supplies required by test/assay.

Step 3. Review visit checklist and ensure site is prepared for visit (procedures, etc). The checklists are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms"

At the visit, the site coordinator should do the following:

Step 1. Ask the participant if he/she has any questions or concerns.

Step 2. Clinical Assessments- use source documents to collect information for each of the clinical assessments. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms"

a. Collect subject's medical history (any changes since last visit)
b. Ask the subject about his/her concomitant medications (changes since last visit)
c. Conduct a directed physical exam prior to administration of study drug injection if clinically indicated
d. Obtain information about Diabetes Management
e. Ask the participant if they have experienced any adverse events

Step 3. Tests and Assays- follow instructions in section 6.4 of this document for collection of specimens

a. Conduct a Urine Pregnancy Test if participant is female of childbearing potential. ******Important: If a participant has a positive Urine Pregnancy Test please discontinue MMTT(s) and study drug administration and proceed to section 6.7 page 76 for additional guidance.***

b. Conduct a 2-hour MMTT *refer to section 6.4.3 and appendix A for details*

c. Collect blood for:

i. EBV Viral Load (EBV/PCR) – for participants Seronegative at screening ONLY
ii. Serum – PK/Cytokine **pre** and **post** injection samples

Step 4. Protocol-Specific Activities: administer **second** dose of study agent. Use source documents to collect information for the administration of study drug. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms". *Please remember to collect the PK/Cytokine post dose sample **1 hour** post injection.* *****Note: this PK sample is the second PK blood draw for this visit. The first PK blood draw should be done before the injection of study drug.***

Step 5. Subject should remain at study site for observation for at least 1 hour following study drug administration

Step 6. Remind subject to bring blood glucose and insulin records to next visit

Step 7. Enter data collected (as applicable) on source documents into the e-CRF(s) online.

Step 8. Scan barcodes for each test/assay into the online specimen collection form(s)

Step 9. Ship specimens to lab(s) using the online shipment system- follow instructions in section 6.4 of this document for packaging and shipment of specimens.

Step 10. Retain all materials from visit and source documents in an organized fashion in a secured, double-locked room.

5.5 Visit 3 Month 2 (Baseline + 2 month):

Window: +/- 7 days

Prior to the visit, the site coordinator should do the following:

Step 1. Schedule the participant for the visit.

Step 2. Notify site pharmacy of visit (date) and inform pharmacy of randomization number for the participant.

Step 3. Order any supplies needed for the visit through the online Fisher supply ordering system. See section 6.4 for a list of supplies required by test/assay

Step 4. Review visit checklist and ensure site is prepared for visit (procedures, etc). The checklists are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms"

At the visit, the site coordinator should do the following:

Step 1. Ask the participant if he/she has any questions or concerns.

Step 2. Clinical Assessments- use source documents to collect information for each of the clinical assessments. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms"

a. Collect subject's medical history (any changes since last visit)
b. Ask the subject about his/her concomitant medications (changes since last visit)
c. Conduct a directed physical exam prior to administration of study drug injection if clinically indicated
d. Obtain information about Diabetes Management
e. Ask the participant if they have experienced any adverse events

Step 3. Tests and Assays- follow instructions in section 6.4 of this document for collection of specimens

a. Conduct a Urine Pregnancy Test if participant is female of childbearing potential
b. Collect blood for:
   i. EBV Viral Load (EBV/PCR) – for participants Seronegative at screening ONLY
   ii. *If applicable,* Pre flu vaccination serology (post flu vaccination serology would then be collected at visit 4 month 3)
   iii. Serum – PK/Cytokine **pre** and **post** injection samples

Step 4. Protocol-Specific Activities: administer **third** dose of study agent. Use source documents to collect information for the administration of study drug. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms". *Please remember to collect the PK/Cytokine post dose sample **1 hour** post injection. ****Note: this PK sample is the second PK blood draw for this visit. The first PK blood draw should be done before the injection of study drug.***

Step 5. At any time after visit 3 study drug administration until visit 12 inclusive, subjects will receive their annual clinically indicated killed flu vaccine at the appropriate time of year. Response to these immunizations will be determined through analysis of a pre flu vaccination serology sample obtained prior to the administration of the flu vaccine. Post flu vaccination serology sample would be obtained at the next scheduled study visit. See Appendix F for more guidance from the CDC per flu vaccination. *****Note vaccinations should be administered after samples are collected and study drug has been administered.***

Step 6. Subject should remain at study site for observation for at least 1 hour following study drug administration (*For all subsequent treatment visits subject should remain at the study site for observation for at least 15 minutes after the study drug administration)*

Step 7. Enter data collected on source documents into the e-CRF(s) online.

Step 8. Scan barcodes for each test/assay into the online specimen collection form(s)

Step 9. Ship specimens to lab(s) using the online shipment system- follow instructions in section 6 of this document for packaging and shipment of specimens.

Step 10. Retain all materials from visit and source documents in an organized fashion in a secured, double-locked room.

5.6 Visit 4 Month 3 (Baseline + 3 months):

Window: +/- 7 days

Prior to visit, the site coordinator should do the following:

Step 4. Schedule the participant for the visit. **Remind the participant that they need to be fasting for this visit.**

Step 5. Order any supplies needed for the visit through the online Fisher supply ordering system. See section 6.4 for a list of supplies required by test/assay

Step 6. Review visit checklist and ensure site is prepared for visit (procedures, etc). The checklists are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms"

At the visit, the site coordinator should do the following:

Step 1. Ask the participant if he/she has any questions or concerns.

Step 2. Clinical Assessments- use source documents to collect information for each of the clinical assessments. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms"

a. Collect subject's medical history (any changes since last visit)
b. Ask the subject about his/her concomitant medications (changes since last visit)
c. Conduct a routine physical exam prior to administration of study drug injection
d. Obtain information about Diabetes Management
e. Ask the participant if they have experienced any adverse events

Step 3. Tests and Assays- follow instructions in section 6.4 of this document for collection of specimens

a. Conduct a Urine Pregnancy Test if participant is female of childbearing potential
b. Conduct a 2 hour MMTT
c. Collect blood for:
    i. EBV Viral Load (EBV/PCR) – for participants Seronegative at screening ONLY
    ii. HbA1c
    iii. *If applicable,* Post flu vaccination serology
    iv. Serum – PK/Cytokine **pre** injection sample
    v. Mechanistic Assessments-
        - Mechanistic Serum
        - Serum – Cytokines
        - Serum – Immunogenicity
        - Whole Blood – RNA

Step 4. Protocol -Specific Activities: administer **fourth** dose of study agent. Use source documents to collect information for the administration of study drug. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms."

Step 5. Remind subject to bring blood glucose and insulin records to next visit

Step 6. Subject should remain at study site for observation for at least 15 minutes following study drug administration

Step 7. Have participant and/or parent (guardian) complete Initial Participant Survey and/or Parent Survey. For additional details please refer to section 6.3.5

Step 8. Enter data collected (as applicable) on source documents into the e-CRF(s) online.

Step 9. Scan barcodes for each test/assay into the online specimen collection form(s)

Step 10. Ship specimens to lab(s) using the online shipment system- follow instructions in section 6.4 of this document for packaging and shipment of specimens.

Step 11. Retain all materials from visit and source documents in an organized fashion in a secured, double-locked room.

5.7 Visit 5 Month 4 (Baseline + 4 months):

Window: +/- 7 days

Prior to the visit, the site coordinator should do the following:

Step 1. Schedule the participant for the visit.

Step 2. Notify site pharmacy of visit (date) and inform pharmacy of randomization number for the participant.

Step 3. Order any supplies needed for the visit through the online Fisher supply ordering system. See section 6.4 for a list of supplies required by test/assay

Step 4. Review visit checklist and ensure site is prepared for visit (procedures, etc). The checklists are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

At the visit, the site coordinator should do the following:

Step 1. Ask the participant if he/she has any questions or concerns.

Step 2. Clinical Assessments- use source documents to collect information for each of the clinical assessments. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

a. Collect subject’s medical history (any changes since last visit)
b. Ask the subject about his/her concomitant medications (changes since last visit)
c. Conduct a directed physical exam prior to administration of study drug injection if clinically indicated
d. Obtain information about Diabetes Management
e. Ask the participant if they have experienced any adverse events

Step 3. Tests and Assays- follow instructions in section 6.4 of this document for collection of specimens

a. Conduct a Urine Pregnancy Test if participant is female of childbearing potential
b. Collect blood for:
    i. EBV Viral Load (EBV/PCR) – for participants Seronegative at screening ONLY

Step 4. Protocol-Specific Activities: administer **fifth** dose of study agent. Use source documents to collect information for the administration of study drug. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

Step 5. Remind subject to bring blood glucose and insulin records to next visit

Step 6. Subject should remain at study site for observation for at least 15 minutes following study drug administration

Step 7. Enter data collected on source documents into the e-CRF(s) online.

Step 8. Scan barcodes for each test/assay into the online specimen collection form(s)

Step 9. Ship specimens to lab(s) using the online shipment system- follow instructions in section 6.4 of this document for packaging and shipment of specimens.

Step 10. Retain all materials from visit and source documents in an organized fashion in a secured, double-locked room.

5.8 Visit 6 Month 5 (Baseline + 5 months):

Window: +/- 7 days

Prior to visit, the site coordinator should do the following:

Step 1. Schedule the participant for the visit.

Step 2. Order any supplies needed for the visit through the online Fisher supply ordering system. See section 6.4 for a list of supplies required by test/assay

Step 3. Review visit checklist and ensure site is prepared for visit (procedures, etc). The checklists are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

At the visit, the site coordinator should do the following:

Step 1. Ask the participant if he/she has any questions or concerns.

Step 2. Clinical Assessments- use source documents to collect information for each of the clinical assessments. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

a. Collect subject’s medical history (any changes since last visit)
b. Ask the subject about his/her concomitant medications (changes since last visit)
c. Conduct a directed physical exam prior to administration of study drug injection if clinically indicated
d. Obtain information about Diabetes Management
e. Ask the participant if they have experienced any adverse events

Step 3. Tests and Assays- follow instructions in section 6.4 of this document for collection of specimens

a. Collect blood for:
    i. EBV Viral Load (EBV/PCR) – for participants Seronegative at screening ONLY
    i. Serum – PK/Cytokine **pre** injection sample
    ii. Mechanistic Assessments-
        1. Mechanistic Serum
        2. Serum – Cytokines
        3. Serum – Immunogenicity

Step 4. Protocol-Specific Activities: administer **sixth** dose of study agent. Use source documents to collect information for the administration of study drug. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

Step 5. Enter data collected (as applicable) on source documents into the e-CRF(s) online.

Step 6. Subject should remain at study site for observation for at least 15 minutes following study drug administration

Step 7. Scan barcodes for each test/assay into the online specimen collection form(s)

Step 8. Ship specimens to lab(s) using the online shipment system- follow instructions in section 6.4 of this document for packaging and shipment of specimens.

Step 9. Retain all materials from visit and source documents in an organized fashion in a secured, double-locked room.

5.9 The following visit is an <u>OPTIONAL</u> visit that the participant should consent to participant in or opt out of when signing the intervention consent

****Visit 6a (Baseline + 5 months & 1week):***
Window: +/- 2 days

<u>Prior to the visit</u>, the site coordinator should do the following:

Step 1. Schedule the participant for the visit. **Remind the participant that they need to be fasting for this visit.**

Step 2. Complete online PRN Optional Visit 6a form. Please document the answers to the questions on this e-CRF in your source documentation.

Step 3. Order any supplies needed for the visit through the online Fisher supply ordering system. See section 6.4 for a list of supplies required by test/assay

Step 4. Review visit checklist and ensure site is prepared for visit (procedures, etc). The checklists are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

<u>At the visit,</u> the site coordinator should do the following:

Step 1. Ask the participant if he/she has any questions or concerns.

Step 2. Clinical Assessments- use source documents to collect information for each of the clinical assessments. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

Step 3. Tests and Assays- follow instructions in section 6.4 of this document for collection of specimens
a. Conduct a 2-hour MMTT

Step 4. Remind subject to bring blood glucose and insulin records to next visit

Step 5. Enter data collected on source documents into the e-CRF(s) online (PRN).

Step 6. Subject should remain at study site for observation for at least 15 minutes following study drug administration

Step 7. Scan barcodes for each test/assay into the online specimen collection form(s)

Step 8. Ship specimens to lab(s) using the online shipment system- follow instructions in section 6.4 of this document for packaging and shipment of specimens.

Step 9. Retain all materials from visit and source documents in an organized fashion in a secured, double-locked room.

5.10 Visit 7 Month 6 (Baseline + 6 months):

Window: +/- 7 days

Prior to the visit, the site coordinator should do the following:

Step 1. Schedule the participant for the visit. **Remind the participant that they need to be fasting for this visit.**

Step 2. Order any supplies needed for the visit through the online Fisher supply ordering system. See section 6.4 for a list of supplies required by test/assay

Step 3. Review visit checklist and ensure site is prepared for visit (procedures, etc). The checklists are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms"

At the visit, the site coordinator should do the following:

Step 1. Ask the participant if he/she has any questions or concerns.

Step 2. Clinical Assessments- use source documents to collect information for each of the clinical assessments. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms"

a. Collect subject's medical history (any changes since last visit)
b. Ask the subject about his/her concomitant medications (changes since last visit)
c. Conduct a routine physical exam prior to administration of study drug injection
d. Obtain information about Diabetes Management
e. Ask the participant if they have experienced any adverse events

Step 3. Tests and Assays- follow instructions in section 6.4 of this document for collection of specimens

a. Conduct a 2-hour MMTT *refer to section 6.4.3 and appendix A for details*
a. Collect blood for:
    i. CBC with Differential
    ii. Chemistries
    i. EBV Viral Load (EBV/PCR) – for participants Seronegative at screening ONLY
    iii. HbA1c
    iv. Mechanistic Assessments –
        1. Mechanistic Serum
        2. Serum – Cytokines
        3. Serum – Immunogenicity
        4. Whole Blood – Plasma/PBMC
        5. Whole Blood – RNA

Step 4. Protocol-Specific Activities: administer **seventh** dose of study agent. Use source documents to collect information for the administration of study drug. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms"

Step 5. Remind subject to bring blood glucose and insulin records to next visit

Step 6. Subject should remain at study site for observation for at least 15 minutes following study drug administration

Step 7. Enter data collected on source documents into the e-CRF(s) online.

Step 8. Scan barcodes for each test/assay into the online specimen collection form(s)

Step 9. Ship specimens to lab(s) using the online shipment system- follow instructions in section 6.4 of this document for packaging and shipment of specimens.

Step 10. Retain all materials from visit and source documents in an organized fashion in a secured, double-locked room.

5.11 Visit 8 Month 7 (Baseline + 7 months):

Window: +/- 7 days

Prior to the visit, the site coordinator should do the following:

Step 1. Schedule the participant for the visit.

Step 2. Order any supplies needed for the visit through the online Fisher supply ordering system. See section 6.4 for a list of supplies required by test/assay

Step 3. Review visit checklist and ensure site is prepared for visit (procedures, etc). The checklists are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

At the visit, the site coordinator should do the following:

Step 1. Ask the participant if he/she has any questions or concerns.

Step 2. Clinical Assessments- use source documents to collect information for each of the clinical assessments. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

a. Collect subject’s medical history (any changes since last visit)
b. Ask the subject about his/her concomitant medications (changes since last visit)
c. Conduct a directed physical exam prior to administration of study drug injection if clinically indicated
d. Obtain information about Diabetes Management
e. Ask the participant if they have experienced any adverse events

Step 3. Tests and Assays- follow instructions in section 6.4 of this document for collection of specimens

a. Conduct a Urine Pregnancy Test if participant is female of childbearing potential
b. Collect blood for:
    i. EBV Viral Load (EBV/PCR) – for participants Seronegative at screening ONLY

Step 4. Protocol-Specific Activities: administer **eighth** dose of study agent. Use source documents to collect information for the administration of study drug. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

Step 5. Remind subject to bring blood glucose and insulin records to next visit

Step 6. Subject should remain at study site for observation for at least 15 minutes following study drug administration

Step 7. Enter data collected on source documents into the e-CRF(s) online.

Step 8. Scan barcodes for each test/assay into the online specimen collection form(s)

Step 9. Ship specimens to lab(s) using the online shipment system- follow instructions in section 6.4 of this document for packaging and shipment of specimens.

Step 10. Retain all materials from visit and source documents in an organized fashion in a secured, double-locked room.

5.12 Visit 9 Month 8 (Baseline + 8 months):

Window: +/- 7 days

Prior to the visit, the site coordinator should do the following:

Step 1. Schedule the participant for the visit.

Step 2. Order any supplies needed for the visit through the online Fisher supply ordering system. See section 6.4 for a list of supplies required by test/assay

Step 3. Review visit checklist and ensure site is prepared for visit (procedures, etc). The checklists are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

At the visit, the site coordinator should do the following:

Step 1. Ask the participant if he/she has any questions or concerns.

Step 2. Clinical Assessments- use source documents to collect information for each of the clinical assessments. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

a. Collect subject’s medical history (any changes since last visit)
b. Ask the subject about his/her concomitant medications (changes since last visit)
c. Conduct a directed physical exam prior to administration of study drug injection if clinically indicated
d. Obtain information about Diabetes Management
e. Ask the participant if they have experienced any adverse events

Step 3. Tests and Assays- follow instructions in section 6.4 of this document for collection of specimens

a. Conduct a Urine Pregnancy Test if participant is female of childbearing potential
b. Collect blood for:
    i. EBV Viral Load (EBV/PCR) – for participants Seronegative at screening ONLY

Step 4. Protocol-Specific Activities: administer **ninth** dose of study agent. Use source documents to collect information for the administration of study drug. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

Step 5. Remind subject to bring blood glucose and insulin records to next visit

Step 6. Subject should remain at study site for observation for at least 15 minutes following study drug administration

Step 7. Enter data collected on source documents into the e-CRF(s) online.

Step 8. Scan barcodes for each test/assay into the online specimen collection form(s)

Step 9. Ship specimens to lab(s) using the online shipment system- follow instructions in section 6.4 of this document for packaging and shipment of specimens.

Step 10. Retain all materials from visit and source documents in an organized fashion in a secured, double-locked room.

5.13 Visit 10 Month 9 (Baseline + 9 months):

Window: +/- 7 days

Prior to the visit, the site coordinator should do the following:

Step 1. Schedule the participant for the visit. **Remind the participant that they need to be fasting for this visit.**

Step 2. Order any supplies needed for the visit through the online Fisher supply ordering system. See section 6.4 for a list of supplies required by test/assay

Step 3. Review visit checklist and ensure site is prepared for visit (procedures, etc). The checklists are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms"

At the visit, the site coordinator should do the following:

Step 1. Ask the participant if he/she has any questions or concerns.

Step 2. Clinical Assessments- use source documents to collect information for each of the clinical assessments. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms"

a. Collect subject's medical history (any changes since last visit)
b. Ask the subject about his/her concomitant medications (changes since last visit)
c. Conduct a routine physical exam prior to administration of study drug injection
d. Obtain information about Diabetes Management
e. Ask the participant if they have experienced any adverse events

Step 3. Tests and Assays- follow instructions in section 6.4 of this document for collection of specimens

a. Conduct a Urine Pregnancy Test if participant is female of childbearing potential
b. Conduct a 2-hour MMTT
c. Collect blood for:
    i. EBV Viral Load (EBV/PCR) – for participants Seronegative at screening ONLY
    i. HbA1c
    ii. Mechanistic Assessments –
        1. Mechanistic Serum
        2. Serum – Cytokines
        3. Serum – Immunogenicity

Step 4. Protocol-Specific Activities: administer **tenth** dose of study agent. Use source documents to collect information for the administration of study drug. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms"

Step 5. Remind subject to bring blood glucose and insulin records to next visit

Step 6. Subject should remain at study site for observation for at least 15 minutes following study drug administration

Step 7. Enter data collected on source documents into the e-CRF(s) online.

Step 8. Scan barcodes for each test/assay into the online specimen collection form(s)

Step 9. Ship specimens to lab(s) using the online shipment system- follow instructions in section 6.4 of this document for packaging and shipment of specimens.

Step 10. Retain all materials from visit and source documents in an organized fashion in a secured, double-locked room.

5.14 Visit 11 Month 10 (Baseline + 10 months):

Window: +/- 7 days

Prior to the visit, the site coordinator should do the following:

Step 1. Schedule the participant for the visit.

Step 2. Order any supplies needed for the visit through the online Fisher supply ordering system. See section 6.4 for a list of supplies required by test/assay

Step 3. Review visit checklist and ensure site is prepared for visit (procedures, etc). The checklists are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

At the visit, the site coordinator should do the following:

Step 1. Ask the participant if he/she has any questions or concerns.

Step 2. Clinical Assessments- use source documents to collect information for each of the clinical assessments. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

a. Collect subject’s medical history (any changes since last visit)
b. Ask the subject about his/her concomitant medications (changes since last visit)
c. Conduct a directed physical exam prior to administration of study drug injection if clinically indicated
d. Obtain information about Diabetes Management
e. Ask the participant if they have experienced any adverse events

Step 3. Tests and Assays- follow instructions in section 6.4 of this document for collection of specimens

a. Conduct a Urine Pregnancy Test if participant is female of childbearing potential
b. Collect blood for:
    i. EBV Viral Load (EBV/PCR) – for participants Seronegative at screening ONLY

Step 4. Protocol-Specific Activities: administer **eleventh** dose of study agent. Use source documents to collect information for the administration of study drug. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

Step 5. Remind subject to bring blood glucose and insulin records to next visit

Step 6. Subject should remain at study site for observation for at least 15 minutes following study drug administration

Step 7. Enter data collected on source documents into the e-CRF(s) online.

Step 8. Scan barcodes for each test/assay into the online specimen collection form(s)

Step 9. Ship specimens to lab(s) using the online shipment system- follow instructions in section 6.4 of this document for packaging and shipment of specimens.

Step 10. Retain all materials from visit and source documents in an organized fashion in a secured, double-locked room.

5.15 Visit 12 Month 11 (Baseline + 11 months):
Window: +/- 7 days

Prior to the visit, the site coordinator should do the following:

Step 1. Schedule the participant for the visit.

Step 2. Order any supplies needed for the visit through the online Fisher supply ordering system. See section 6.4 for a list of supplies required by test/assay

Step 3. Review visit checklist and ensure site is prepared for visit (procedures, etc). The checklists are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

At the visit, the site coordinator should do the following:

Step 1. Ask the participant if he/she has any questions or concerns.

Step 2. Clinical Assessments- use source documents to collect information for each of the clinical assessments. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

a. Collect subject’s medical history (any changes since last visit)
b. Ask the subject about his/her concomitant medications (changes since last visit)
c. Conduct a directed physical exam prior to administration of study drug injection if clinically indicated
d. Obtain information about Diabetes Management
e. Ask the participant if they have experienced any adverse events

Step 3. Tests and Assays- follow instructions in section 6.4 of this document for collection of specimens

a. Conduct a Urine Pregnancy Test if participant is female of childbearing potential
b. Collect blood for:
    i. EBV Viral Load – EBV PCR (if applicable)
    ii. Pre Tetanus immunization blood draw

Step 4. Protocol-Specific Activities: administer **twelfth and final** dose of study agent. Use source documents to collect information for the administration of study drug. The source documents are located online in the TN14 Protocol Area, folder entitled “TN14 – Forms: Source Documents and Visit Checklists”

Step 5. At study visit 12, subjects will have a pre-immunization blood draw and then receive a tetanus immunization (participants may also receive the killed flu vaccination at this visit which would require a pre and one month post immunization draw)

Step 6. Subject should remain at study site for observation for at least 15 minutes following study drug administration

Step 7. Remind subject to bring blood glucose and insulin records to next visit

Step 8. Enter data collected on source documents into the e-CRF(s) online.

Step 9. Scan barcodes for each test/assay into the online specimen collection form(s)

Step 10. Ship specimens to lab(s) using the online shipment system- follow instructions in section 6.4 of this document for packaging and shipment of specimens.

Step 11. Retain all materials from visit and source documents in an organized fashion in a secured, double-locked room.

5.16 Visit 13 (1 year or Baseline + 12 months):

Window: +/- 7 days

Prior to the visit, the site coordinator should do the following:

Step 1. Schedule the participant for the visit. **Remind the participant that they need to be fasting for this visit.**

Step 2. Order any supplies needed for the visit through the online Fisher supply ordering system. See section 6.4 for a list of supplies required by test/assay

Step 3. Review visit checklist and ensure site is prepared for visit (procedures, etc). The checklists are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms"

At the visit, the site coordinator should do the following:

Step 1. Ask the participant if he/she has any questions or concerns.

Step 2. Clinical Assessments- use source documents to collect information for each of the clinical assessments. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms"

a. Collect subject's medical history (any changes since last visit)
b. Ask the subject about his/her concomitant medications (changes since last visit)
c. Conduct a routine physical exam
d. Obtain information about Diabetes Management
e. Ask the participant if they have experienced any adverse events

Step 3. Tests and Assays- follow instructions in section 6.4 of this document for collection of specimens

a. Conduct a Urine Pregnancy Test if participant is female of childbearing potential
b. Conduct a:
    i. 4 hour MMTT for subjects ≥ 12 years of age at time of screening
    ii. 2-hour MMTT for subjects < 12 years of age at time of screening
c. Collect blood for:
    i. CBC with Differential
    ii. Chemistries
    i. EBV Viral Load (EBV/PCR) – for participants Seronegative at screening ONLY
    iii. Post tetanus immunization follow up blood draw
    iv. HbA1c
    i. Serum – PK/Cytokine sample
    v. Mechanistic Assessments –
        1. Mechanistic Serum
        2. Serum – Cytokines
        3. Serum – Immunogenicity
        4. Whole Blood – Plasma/PBMC
        5. Whole Blood – RNA

Step 4. Remind subject to bring blood glucose and insulin records to next visit

Step 5. Enter data collected on source documents into the e-CRF(s) online.

Step 6. Have participant and/or parent (guardian) complete Follow-up Participant Survey and/or Parent Survey. For additional details please refer to section 6.3.5.

Step 7. Scan barcodes for each test/assay into the online specimen collection form(s)

Step 8. Ship specimens to lab(s) using the online shipment system- follow instructions in section 6.4 of this document for packaging and shipment of specimens.

Step 9. Retain all materials from visit and source documents in an organized fashion in a secured, double-locked room.

5.17 Visit 14 (Month 18):

Window: +/- 14 days

Prior to the visit, the site coordinator should do the following:

Step 1. Schedule the participant for the visit.

Step 2. Order any supplies needed for the visit through the online Fisher supply ordering system. See section 6.4 for a list of supplies required by test/assay

Step 3. Review visit checklist and ensure site is prepared for visit (procedures, etc). The checklists are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

At the visit, the site coordinator should do the following:

Step 1. Ask the participant if he/she has any questions or concerns.

Step 2. Clinical Assessments- use source documents to collect information for each of the clinical assessments. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

a. Collect subject’s medical history (any changes since last visit)
b. Ask the subject about his/her concomitant medications (changes since last visit)
c. Conduct a routine physical exam
d. Obtain information about Diabetes Management
e. Ask the participant if they have experienced any adverse events

Step 3. Tests and Assays- follow instructions in section 6.4 of this document for collection of specimens

a. Conduct a Urine Pregnancy Test if participant is female of childbearing potential
b. Conduct a 2-hour MMTT
c. Collect blood for:
    i. HbA1c
    i. Serum – PK/Cytokine sample
    ii. Mechanistic Assessments –
        1. Mechanistic Serum
        2. Serum – Cytokines
        3. Serum – Immunogenicity

Step 4. Remind subject to bring blood glucose and insulin records to next visit

Step 5. Enter data collected on source documents into the e-CRF(s) online.

Step 6. Scan barcodes for each test/assay into the online specimen collection form(s)

Step 7. Ship specimens to lab(s) using the online shipment system- follow instructions in section 6.4 of this document for packaging and shipment of specimens.

5.18 Visit 15 (2 years or 24 months):

Window: +/- 14 days

Prior to the visit, the site coordinator should do the following:

Step 1. Schedule the participant for the visit. **Remind the participant that they need to be fasting for this visit.**

Step 2. Order any supplies needed for the visit through the online Fisher supply ordering system. See section 6.4 for a list of supplies required by test/assay

Step 3. Review visit checklist and ensure site is prepared for visit (procedures, etc). The checklists are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms"

At the visit, the site coordinator should do the following:

Step 1. Ask the participant if he/she has any questions or concerns.

Step 2. Clinical Assessments- use source documents to collect information for each of the clinical assessments. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms"

a. Collect subject's medical history (any changes since last visit)
b. Ask the subject about his/her concomitant medications (changes since last visit)
c. Conduct a routine physical exam
d. information about Diabetes Management
e. Ask the participant if they have experienced any adverse events

Step 3. Tests and Assays- follow instructions in section 6.4 of this document for collection of specimens

a. Conduct a Urine Pregnancy Test if participant is female of childbearing potential
b. Conduct a:
    i. 4 hour MMTT for subjects $\geq$ 12 years of age at screening
    ii. 2-hour MMTT for subjects < 12 years of age at screening
c. Collect blood for:
    i. HbA1c
    ii. EBV Viral Load (EBV/PCR) – for participants Seronegative at screening ONLY
    iii. Mechanistic Assessments –
        1. Mechanistic Serum
        2. Serum – Cytokines
        3. Serum – Immunogenicity
        4. Whole Blood – Plasma/PBMC
        5. Whole Blood – RNA

Step 4. Remind subject to bring blood glucose and insulin records to next visit

Step 5. Enter data collected on source documents into the e-CRF(s) online.

Step 6. Scan barcodes for each test/assay into the online specimen collection form(s)

Step 7. Ship specimens to lab(s) using the online shipment system- follow instructions in section 6.4 of this document for packaging and shipment of specimens.

FOLLOW UP AFTER 24 MONTHS
****Visits will be conducted approximately every 6 months***

5.19 Visit 16 (30 months):
Window: +/- 14 days

Prior to the visit, the site coordinator should do the following:

Step 1. Schedule the participant for the visit.

Step 2. Order any supplies needed for the visit through the online Fisher supply ordering system. See section 6.4 for a list of supplies required by test/assay

Step 3. Review visit checklist and ensure site is prepared for visit (procedures, etc). The checklists are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms"

At the visit, the site coordinator should do the following:

Step 1. Ask the participant if he/she has any questions or concerns.

Step 2. Clinical Assessments- use source documents to collect information for each of the clinical assessments. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled "TN14 – (C): Forms"

a. Collect subject's medical history (any changes since last visit)
b. Ask the subject about his/her concomitant medications (changes since last visit)
c. Conduct a routine physical exam
d. Obtain information about Diabetes Management
e. Ask the participant if they have experienced any adverse events

Step 3. Tests and Assays- follow instructions in section 6.4 of this document for collection of specimens

a. Conduct a Urine Pregnancy Test if participant is female of childbearing potential
b. Conduct a 2-hour MMTT
c. Collect blood for:
    i. HbA1c
    ii. Mechanistic Assessments –
        1. Mechanistic Serum
        2. Serum – Cytokines
        3. Serum – Immunogenicity

Step 4. Subsequent visits

a. If there is still detectable C-peptide the participant would continue on subsequent visit # 17 (36 months)
b. If there is no detectable C-peptide the participant would continue on subsequent visit # 17 (36 months) but would no longer have an MMTT conducted for the remainder of the study

Step 5. Remind subject to bring blood glucose and insulin records to next visit

Step 6. Enter data collected on source documents into the e-CRF(s) online.

Step 7. Scan barcodes for each test/assay into the online specimen collection form(s)

Step 8. Ship specimens to lab(s) using the online shipment system- follow instructions in section 6.4 of this document for packaging and shipment of specimens.

5.20 Visit 17 (36 months):

Window: +/- 14 days

Prior to the visit, the site coordinator should do the following:

Step 1. Schedule the participant for the visit.

Step 2. Order any supplies needed for the visit through the online Fisher supply ordering system. See section 6.4 for a list of supplies required by test/assay

Step 3. Review visit checklist and ensure site is prepared for visit (procedures, etc). The checklists are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

At the visit, the site coordinator should do the following:

Step 1. Ask the participant if he/she has any questions or concerns.

Step 2. Clinical Assessments- use source documents to collect information for each of the clinical assessments. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

a. Collect subject’s medical history (any changes since last visit)
b. Ask the subject about his/her concomitant medications (changes since last visit)
c. Conduct a routine physical exam
d. Obtain information about Diabetes Management
e. Ask the participant if they have experienced any adverse events

Step 3. Tests and Assays- follow instructions in section 6.4 of this document for collection of specimens

a. Conduct a Urine Pregnancy Test if participant is female of childbearing potential
b. Conduct a 2-hour MMTT
c. Collect blood for:
    i. HbA1c
    ii. Mechanistic Assessments
        1. Mechanistic Serum
        2. Serum – Cytokines
        3. Serum – Immunogenicity

Step 4. Subsequent visits

a. If there is still detectable C-peptide the participant would continue on subsequent visit # 18 (3 years or 42 months)
b. If there is no detectable C-peptide the participant would continue on subsequent visit # 18 (3 years or 42 months) but would no longer have an MMTT conducted for the remainder of the study

Step 5. Remind subject to bring blood glucose and insulin records to next visit

Step 6. Enter data collected on source documents into the e-CRF(s) online.

Step 7. Scan barcodes for each test/assay into the online specimen collection form(s)

Step 8. Ship specimens to lab(s) using the online shipment system- follow instructions in section 6.4 of this document for packaging and shipment of specimens.

5.21 Visit 18 (3 years or 42 months):

Window: +/- 14 days

Prior to the visit, the site coordinator should do the following:

Step 1. Schedule the participant for the visit.

Step 2. Order any supplies needed for the visit through the online Fisher supply ordering system. See section 6.4 for a list of supplies required by test/assay

Step 3. Review visit checklist and ensure site is prepared for visit (procedures, etc). The checklists are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

At the visit, the site coordinator should do the following:

Step 1. Ask the participant if he/she has any questions or concerns.

Step 2. Clinical Assessments- use source documents to collect information for each of the clinical assessments. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

a. Collect subject’s medical history (any changes since last visit)
b. Ask the subject about his/her concomitant medications (changes since last visit)
c. Conduct a routine physical exam
d. Obtain information about Diabetes Management
e. Ask the participant if they have experienced any adverse events

Step 3. Tests and Assays- follow instructions in section 6.4 of this document for collection of specimens

a. Conduct a Urine Pregnancy Test if participant is female of childbearing potential
b. Conduct a 2-hour MMTT
c. Collect blood for:
    i. HbA1c
    ii. Mechanistic Assessments
        1. Mechanistic Serum
        2. Serum – Cytokines
        3. Serum – Immunogenicity

Step 4. Subsequent visits

a. If there is still detectable C-peptide the participant would continue on subsequent visit # 19 (4 years or 48 months)
b. If there is no detectable C-peptide the participant would continue on subsequent visit # 19 (4 years or 48 months)but would no longer have an MMTT conducted for the remainder of the study

Step 5. Remind subject to bring blood glucose and insulin records to next visit

Step 6. Enter data collected on source documents into the e-CRF(s) online.

Step 7. Scan barcodes for each test/assay into the online specimen collection form(s)

Step 8. Ship specimens to lab(s) using the online shipment system- follow instructions in section 6.4 of this document for packaging and shipment of specimens.

5.21 Visit 19 (4 years or 48 months):

Window: +/- 14 days

Prior to the visit, the site coordinator should do the following:

Step 1. Schedule the participant for the visit.

Step 2. Order any supplies needed for the visit through the online Fisher supply ordering system. See section 6.4 for a list of supplies required by test/assay

Step 3. Review visit checklist and ensure site is prepared for visit (procedures, etc). The checklists are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

At the visit, the site coordinator should do the following:

Step 1. Ask the participant if he/she has any questions or concerns.

Step 2. Clinical Assessments- use source documents to collect information for each of the clinical assessments. The assessment tools used to record source documentation are located online in the TN14 Protocol Area, folder entitled “TN14 – (C): Forms”

a. Collect subject’s medical history (any changes since last visit)
b. Ask the subject about his/her concomitant medications (changes since last visit)
c. Conduct a routine physical exam
d. Obtain information about Diabetes Management
e. Ask the participant if they have experienced any adverse events

Step 3. Tests and Assays- follow instructions in section 6.4 of this document for collection of specimens

a. Conduct a Urine Pregnancy Test if participant is female of childbearing potential
b. Conduct a 2-hour MMTT
c. Collect blood for:
    i. HbA1c
    ii. Mechanistic Assessments
        4. Mechanistic Serum
        5. Serum – Cytokines
        6. Serum – Immunogenicity

Step 4. Enter data collected on source documents into the e-CRF(s) online.

Step 5. Scan barcodes for each test/assay into the online specimen collection form(s)

Step 6. Ship specimens to lab(s) using the online shipment system- follow instructions in section 6.4 of this document for packaging and shipment of specimens.

Step 7. Proceed to section 5.22.4 – Participant Natural End of Study (all visits completed)

5.22 End of Study Participation

5.22.1 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.

5.22.2 Participant taken off of Treatment but remains on Study

If a participant is taken off of treatment, but will continue to participate in study visits conducted per the protocol, the site should complete an adverse event form if applicable and complete the tracking form for each study treatment visit thereafter. Please ensure that this information is also documented in the participant's source documentation.

5.22.3 Participant Withdrawal, Death, or Lost to Follow-up

A subject is only considered off study if the subject withdraws consent or dies. If a participant has withdrawn consent or died, the site should complete the "Change of Status" e-CRF in the online electronic data capture system and indicate that the subject has withdrawn consent or died.

1. The "Date change in status become effective" should reflect the date the subject withdrew consent or died.
2. Proceed to section B, enter a date of withdrawal or death if appropriate. Indicate the reason for withdrawal: withdrew consent or death.
3. No further e-CRF(s) or visits will be expected in the system for the subject.

A subject is only considered lost to follow-up if the subject misses visit 13 (primary endpoint). If it is determined that a participant is lost to follow-up, the site should complete the "Change of Status" e-CRF in the online electronic data capture system and indicate that the subject has withdrawn consent or died.

1. The "Date change in status become effective" should reflect the date that it was determined the subject is lost to follow-up
2. Proceed to section B, enter a date of withdrawal. Indicate the reason for withdrawal: lost to follow up.
3. No further e-CRF(s) or visits will be expected in the system for the subject.

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

1. The "Date change in status become effective" should reflect the date it was determined the subject rejoined the study
2. Proceed to section C, enter the date of the subject's first visit rejoining the study
3. The subject will rejoin the study according to the time point at which they would currently be should they have remained on the study (for example, if the subject 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).

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

Prior to the visit, the site coordinator should do the following:

Step 1. Schedule the participant for the visit.

Step 2. Contact the TNCC for the end of study report

At the visit, the site coordinator should do the following:

Step 1. Ask the participant if he/she has any questions or concerns.

Step 2. Have participant and/or parent (guardian) complete Final Participant Survey and/or Parent Survey before debriefing the participant. For additional details please refer to section 6.3.5.

Step 3. Provide the subject with the end of study report and answer any questions that they might have.
Note: No CRF's need to be completed for this visit.

6 PROTOCOL DETAILS

6.1 Quizzes

6.1.1 Volunteer Survey (Visit -1 OR Visit 1)

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

Procedure:

Step 1. Give the Survey to the participant following a description of the study and after the Screening Consent has been signed

Note: The Survey should always be given before the Intervention Consent has been signed.

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

Step 3. The site coordinator will review the completed Volunteer Survey with the participant (and his/her parent/guardian in the case of an adolescent participant), taking special care to review any questions the participant answered incorrectly and answer any questions about the study.

Step 13. Please document that you have reviewed the Volunteer Survey with the participant and/or his/her parent/guardian and reviewed in particular any questions the participant answered incorrectly. *See Section 14.5 Assessment Tool for this process and the answer key for the Volunteer Survey in section 14.6.* ***Please note that this assessment tool titled "Volunteer Understanding Assessment Review" is also located online in the TN14 Protocol Area, folder entitled "***TN14 – (C): Forms"

6.2 Protocol-Specific Activities

6.2.1 Randomization/Treatment Assignment (Baseline/Visit 1)

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 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 the following two groups:

- 44 participants will be assigned to receive 12 injections with 2.0 mg/kg to a maximum 300 mg of Canakinumab.
- 22 participants will be assigned to receive 12 injections of placebo.

Participants will be randomized, in approximately equal numbers at sites. The randomization method will be stratified by the TrialNet study site. This approach ensures that the number of treatment group assignment will be approximately balanced within each site.

Neither the TrialNet Coordinating Center (TNCC) nor the participating sites will know the treatment group assignment. The TNCC will maintain the list of participant randomization assignment.

Procedure: At the baseline visit, the site coordinator should check the following prior to randomization/treatment assignment:

Step 1. Be sure the following has occurred:

Step 14. Subject has signed the Screening and Intervention Consent (Screening and Intervention Assent if applicable), *these should be signed before any visit procedures are performed – See section 14.4 for the Assessment Tool for this process.* ***Please note that this assessment tool titled "Documentation of Enrollment_Consent Process" is also located online in the TN14 Protocol Area, folder entitled "***TN14 – (C): Forms"

a. Subject has completed the screening visit and procedures, and
b. Subject has met all of the inclusion criteria and none of the exclusion criteria

If the above criteria are met, proceed to step #2

If the above criteria are not met and the participant is not eligible:

a. If ineligible and participant did not complete the screening visit and you did not ask the participant all the eligibility questions please complete Pre-Randomization Exit form.
b. If ineligible and participant did complete the screening visit and you did ask the participant all the eligibility questions please complete the Eligibility e-CRF.

Step 2. Under the Participant Details Screen, the site coordinator should check if the status for participant reflects Eligible. If status reflects eligible proceed to step #3.

Step 3. Randomize the participant in the online system
Note: Each randomization number will only be assigned once

Step 4. Make note of the randomization number in the source documents.
Note: For further randomization detail please reference the Pharmacy PHO Section 7.0 Additional Details.

**Subjects will not be enrolled who have other active serious medical problems. Frequent monitoring of patients with history, physical examination, and laboratory studies will allow for early identification of adverse events. All participants will be required to have adequate hemoglobin to allow safe frequent venipuncture. If there are any questions or concerns regarding hemoglobin values please contact the medical monitor Brett Loechelt, MD. Every attempt will be made to minimize the number of venipunctures.

All study drug injections will take place in a facility that has resuscitation capabilities, and subjects will be closely monitored during and after the injection.

Subjects will be counseled about the potential risk for infections and the need to report any change in health status between or at the time of visits. Directed questioning about concurrent illness will occur before each injection. No injection will occur in those with signs or symptoms indicative of active infection. In addition, those subjects who were EBV serology negative at screening will undergo evaluation of EBV viral load at each visit (visits 1 thru 13 and 15). If the subject becomes positive (i.e. laboratory evidence of active EBV infection is present), confirmation testing will be done and study medication withheld until absence of signs and symptoms of infection including negative viral load. This will be assessed by follow-up assessments with appropriate clinical test including EBV serology at 2, 4, 8, 12 weeks, and then monthly. In each instance, resumption of injections will occur only after review of the data and consultation with the TrialNet infectious disease consultants. **If applicable, please be sure to complete the PRN Two Week Post Positive EBVPCR Confirmatory Testing e-CRF to ensure that you are appropriately reimbursed.*

6.2.2 Study Drug Administration (Visits 1-12)

Definition: The injection will be a standard subcutaneous injection.

Do not administer in the area that the subject used for insulin injection. No pre-med required. All patients will receive 12 subcutaneous injections of 2.0 mg/kg to maximum of 300 mg Canakinumab or placebo. Subsequent doses will be each calendar month i.e. if the baseline visit occurs on November 15th target dates for each subsequent treatment visit will be December 15th (visit 2, month 1), January 15th (visit 3, month 2) etc (visit windows are +/- 7 days of target date). As the first injection is given at baseline (day 0), the last injection will be given on the 11th month into the study. Dosing will not be done in subjects with a febrile illness (a nonspecific illness characterized by a sudden onset of fever where fever is $\geq$ 101°F)

within the previous 48 hours or other signs or symptoms of active infection (such as a sore throat). These subjects will be rescheduled for another day within study dosing window. For this reason sites are encouraged to schedule their participant's visits for the first day of the visit window if at all possible. If the patient remains ill during the study window, that dose will be skipped and the patient will wait until the next scheduled dose.

Procedure:

Step 1. Provide to the site pharmacist:

a. The participant ID
b. The randomization number assigned to the participant
c. The visit time point

Step 2. The site pharmacist will:

d. Log the participant ID, randomization number, vial # dispensed on to the Pharmacy Agent Accountability Log (page 27 of the Pharmacy Manual)
e. Dispense to the site coordinator from the appropriate treatment kit the appropriate vial and syringe for the appropriate visit/subcutaneous injection. The dose is administered based on body weight, and the value will be rounded up for any decimal to the next whole number; i.e., (whether weight is 45.1 or 45.6 kg weight will be rounded up to 46 kg). **Weight from the previous visit may be used so the pharmacy can prepare the dose ahead of time for all visits except the baseline visit which will be based on the subject's weight at the baseline visit. There are additional details as well as a table for determining dose administration by weight in the TN14 pharmacy manual.**

Step 3. Prepare the syringe:

a. The pharmacist will prepare the syringe. The individual preparing and the individual who is administering the study agent should be a qualified person delegated the responsibility by the site PI. The syringe provided by the pharmacist will be a 1.0mL graduated disposable syringe (two 1.0mL graduated disposable syringes may be provided if applicable). The syringe should be prepared immediately prior to study agent administration. If it is not used within 60 minutes of preparation, it should be kept at 2-8°C as chemical and physical in-use stability has been demonstrated for a maximum of 24 hours at 2 to 8°C. If the vial must be stored on wet ice, direct contact to the ice must be prevented to avoid uncontrolled local freezing. The vials should be allowed to come to room temperature for 5-10 minutes but not more than 15 minutes before administration.
b. Study drug preparation is provided in the Pharmacy Manual for site Pharmacists.

Step 4. Administer study substance to participant.

a. Administer drug at a (physical) location where professionals are on hand to respond to any problems that may occur such as anaphylaxis
b. Utilize sterile technique
c. Swab the injection site with an alcohol pad
d. Administer injection as standard subcutaneous injection

Note: It is not advisable to administer the injection in the area or the same site as the subject uses for insulin injection

e. Give subject the entire dose
f. Provide slight pressure to the injection site after administration with a cotton ball or gauze pad
g. All injection site or related adverse events can be treated as needed (warmth, redness, pain, swelling, itching).
h. Patients should remain at the study site for observation for at least 1 hour following study drug administration for the first three doses. For the subsequent times, patients should remain at the study site for observation for at least 15 minutes after the study drug administration

Step 5. Complete online e-CRF(s)

a. FOR BASELINE VISIT: Complete the e-CRF: Treatment Start Date
b. FOR ALL STUDY DRUG ADMINISTRATION VISITS INCLUDING BASELINE: Complete e-CRF: Study Drug Administration form

*****IMPORTANT NOTE: If study agent is mishandled and storage of study agent procedures as detailed in the pharmacy MOO are not followed please inform the Central Pharmacy EMINENT & the protocol CRA. In addition to the correspondence specified above please place a note to file per the incident in both the pharmacy and regulatory binders.**

6.2.3 AE (Adverse Event) Assessment (All visits except Screening Visit 0)

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

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

Reportable Adverse Event: defined per protocol For TN14, only AE's determined to be CTCAE Version 3.0 grade 2 or greater are reportable. All AE(s) that are serious infections and are regarded as SAE(s) the events are reportable through AEDAMS and to the FDA even if the event is an SAE and does not answer yes to all the following questions:

- Is the adverse event unexpected?
- Is the adverse event related or possibly related to participation in the research?
- Does the adverse event suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized?

TrialNet Reporting Timeline:

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

  -OR-
  - Is Unexpected/Unanticipated
- All other (suspected) reportable AEs and SAE(s) which do not meet the 24 hour reporting criteria must be reported to TrialNet within **20 working days** of the notification of the event or of the site becoming aware of the event.

Procedure:

Step 1. Utilize source document as 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 new symptom is grade 2 or greater or worsening symptoms since last visit (pre-existing conditions) have increased in severity (i.e. grade 1 prior to start of treatment or last visit, now a grade 2 at current visit)

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

Step 5. If AE is an SAE which the investigators judge as probably or definitely related to study agent and the event is not expected, the coordinator should complete Medwatch FORM FDA3500A, submit to the FDA, and immediately fax to the TNCC and the TN Medical Monitor. If an AE event is regarding an infection and is an SAE regardless whether the investigators judge as probably or definitely related, and regardless of whether it is expected, the coordinator should complete a Medwatch Form FDA3500A, submit to the FDA, and immediately fax to the TNCC***. Please refer to section 10 ADVERSE EVENT REPORT PROCEDURES for more in depth guidelines on reporting AE(s) and SAE(s) for the TN14 Anti IL-1Beta protocol specifically.***

6.2.4 Deviations

Definitions:
Protocol Deviation: Any departure from an IRB (Ethics Board) approved study protocol during the conduct of the study. Changes or alterations in the conduct of the trial which do not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data are known as **minor** protocol deviations.

Protocol Violation: Any departure from an IRB approved study protocol during the conduct of the study that may affect the subject's rights, safety, or well being and/or the completeness, accuracy and reliability of the study data. Protocol Violations are also known as **major** protocol deviations

Procedures:
1. Reporting Timeline:
    - Protocol deviations may result from an omission or error by the study team, or by actions of the participant.
    - Deviations (Major) that pose an immediate potential risk to subject safety will be reported to the TNCC within 24 hours of their recognition. Examples of these types of deviations include but are not limited to:
        i. Injection of study medication without a signed informed consent document
        ii. Injection of the incorrect dose of XXXX (Pharmacy error/drug related error)
        iii. Contraindicated medication received
        iv. Ineligible subject randomized (and eligibility committee did not approve)
        v. Allowable blood volume limit exceeded
        vi. Specimen collected in error
        vii. Tolerance Test issue- Tolerance Test conducted although participant was either hypo or hyperglycemic
        viii. Study drug administered when it should have been withheld per protocol
    - Deviations (Minor) that do not pose an immediate potential risk to subject safety will be reported to the TNCC within 10 days. Examples of these types of deviations include but are not limited to:
        i. Absent laboratory data
        ii. Treatment outside of protocol mandated visit windows
        iii. Visit completed outside of allowable window
        iv. Specimen collected outside of allowable visit window
        v. Specimen collection missed
        vi. Visit missed
        vii. Procedure missed
        viii. Study procedure not completed (ex. no physical exam or only completed a limited physical exam when the schedule of assessments required a full physical exam).
        ix. More than 4 weeks lapses from the participant's randomization date to treatment start date.
2. Reporting Process:
    - Deviations will be reported to the TNCC utilizing the Protocol Deviation Form.

*****MPORTANT NOTE:** Local IRB(s) can define what deviations/violations they wanted reported. No matter how the TNCC defines reporting of protocol deviations/violations, the study site/PI are not exempt from following their own institutional/IRB SOP(s) regarding what constitutes appropriate reporting of deviations/violations.

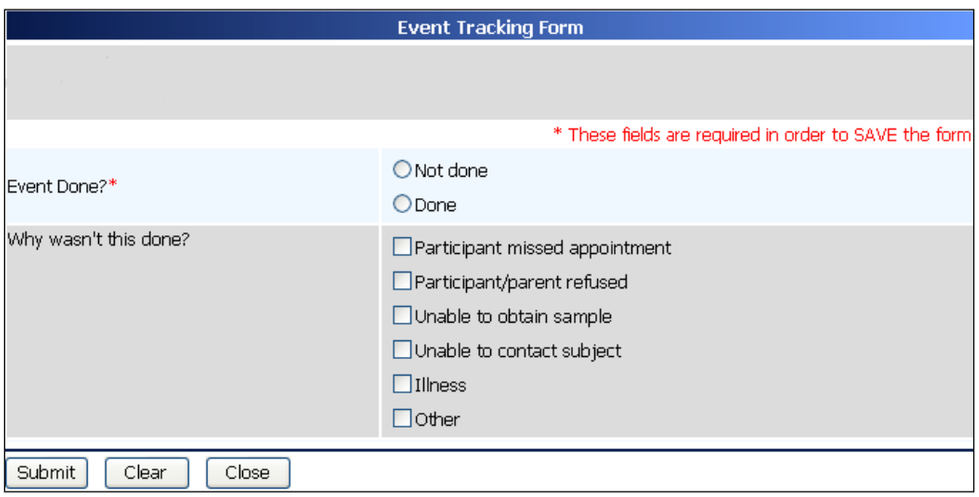
6.2.5 Missed Visits

Definition:
If a participant misses a scheduled visit, every effort should be made to reschedule the visit within the permissible window period surrounding the original visit date. If the visit is rescheduled within this timeframe, no further actions need to be taken, and the visit should go on as planned. For this reason sites are encouraged to schedule their participant's visits for the first day of the visit window if at all possible. If the visit is not rescheduled within this window, every effort should be made to bring the participant into the clinic as soon as possible. Ideally the participant should come in for the visit, even if

they are not going to receive the injection. This will allow for us to check for any adverse events, etc. If the participant comes into the clinic beyond the allowable visit window, a deviation form should be completed and the tracking forms for the missed events should be completed as well indicating the reason for the visit being missed.

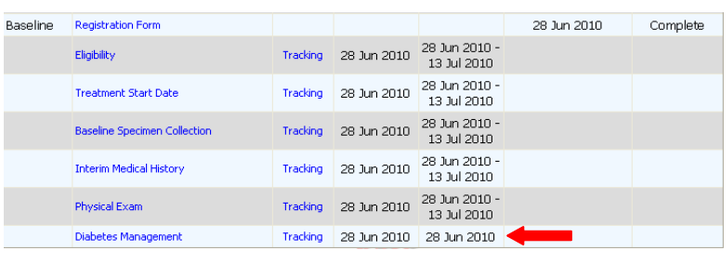
Every effort should be made to contact participants who fail to attend their follow-up visits in order to ensure that they are in satisfactory health and to encourage them to continue with future study follow-up visits. This will entail, at a minimum, three telephone contact attempts and two written attempts with return receipt requests. Research staff at each of the sites is responsible for keeping participant contact information up to date at every study visit. Principal investigators may want to contact the noncompliant participants to encourage them to come into the clinic even if they no longer wish to receive injections. Please document this contact and correspondence in the participant's source documentation. If a participant chooses to discontinue treatment, but plans to continue to come in for follow-up visits then complete a "change in study drug form" (see section 5.22.2). If the participant wishes to discontinue the study altogether or the site PI feels that the participant should be taken off of study due to non-compliance then complete a "change in status form" (see section 5.22.3).

6.2.6 *Tracking Forms*

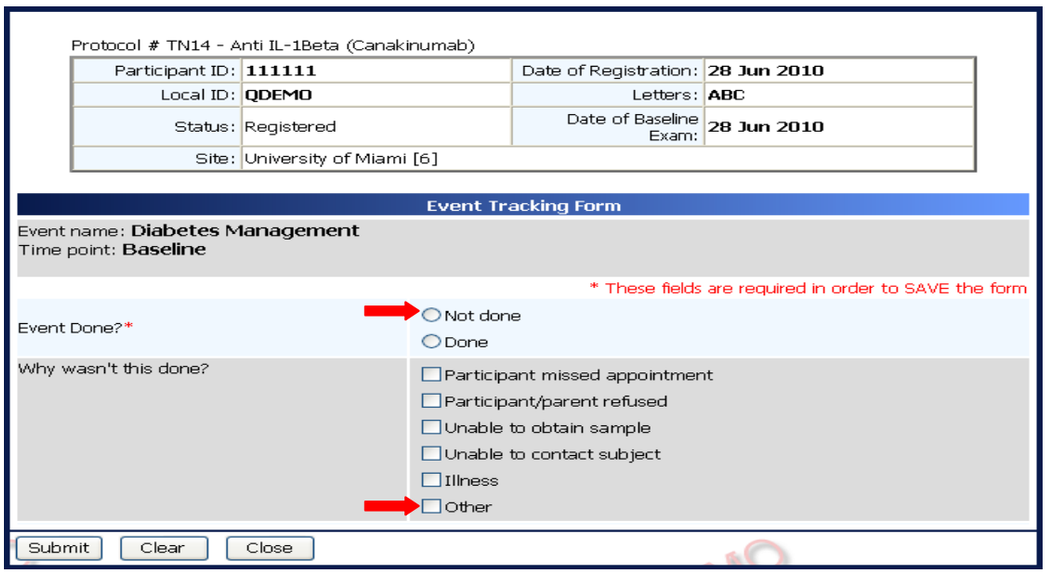


If a visit event is missed or not done please complete the tracking form for that respective event.

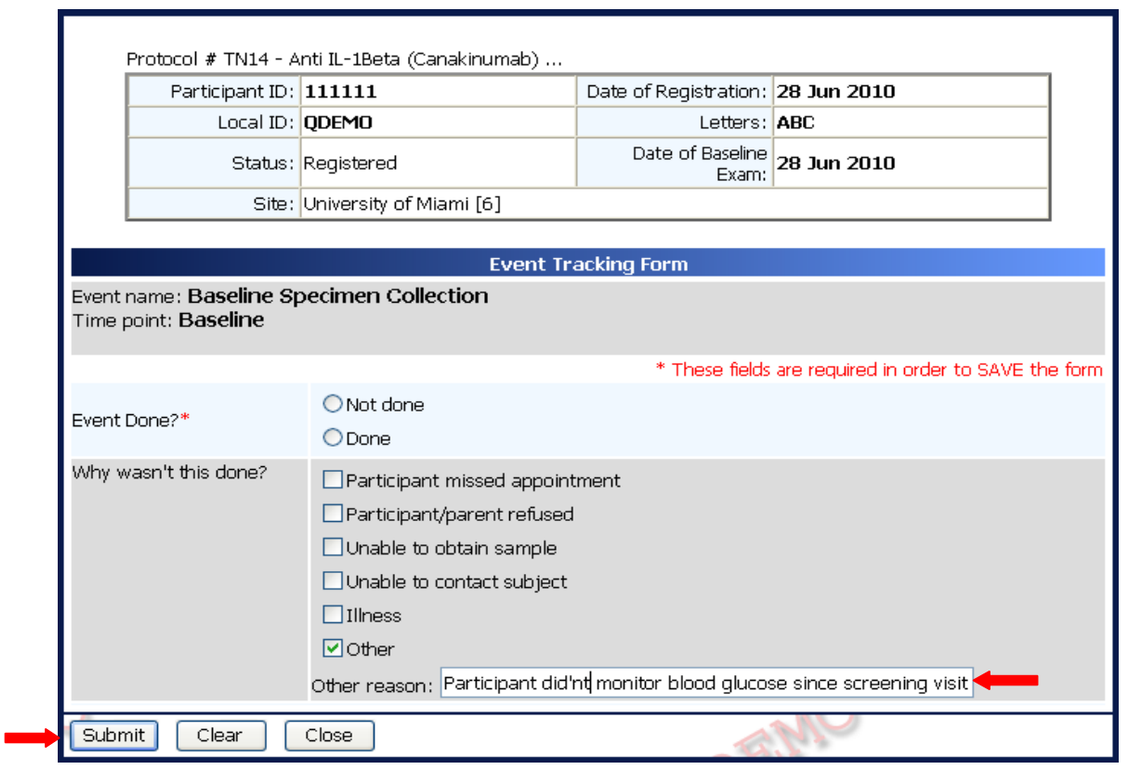
For instance if the baseline visit the participant does not have records of blood glucose/insulin diary since the prior visit the site would select the tracking form for the Diabetes Management event to complete at the baseline visit.



You would select "Not done" and specify the reason why below. In this case it would be "Other".

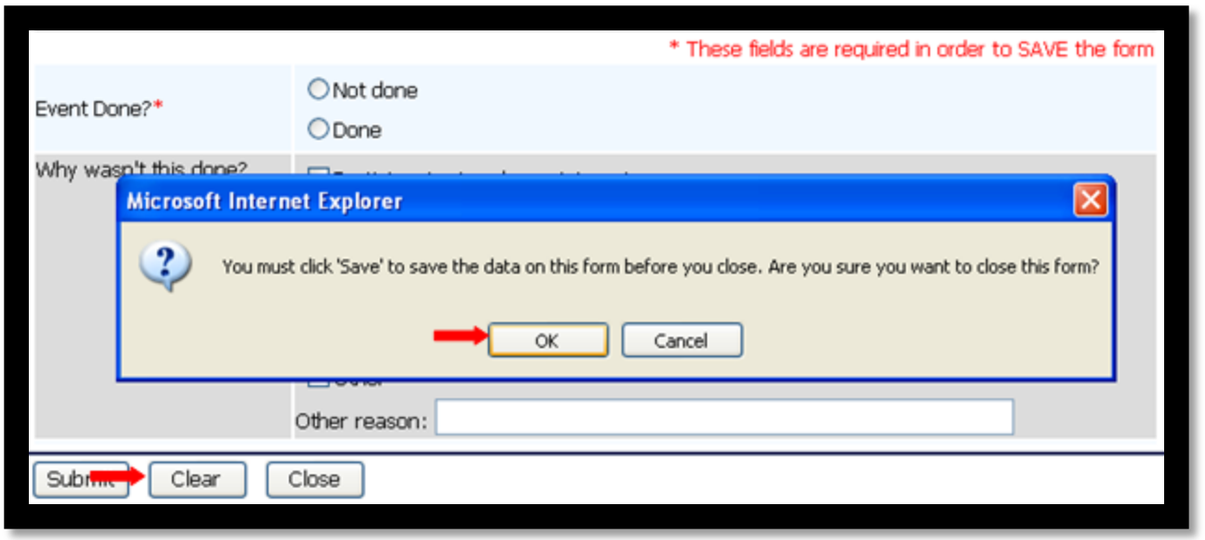


When you select other a comment box opens up for you to specify “Other reason”. Click Submit when done.



If the participant did in fact maintain their blood glucose/insulin records since prior visit the site you can clear the form by selecting the clear button below.

You would then hit okay to save any changes.



**The "Done" option should not be used unless you are awaiting information such as diabetes management information. Please contact the protocol CRA before using the "Done" option. All visit forms should be completed within 30 days of visit date.

6.2.7 Intensive Diabetes Management

During the study, all participants will receive intensive management of their diabetes. The goal of treatment will be to keep the hemoglobin A1c level (HbA1c) as close to normal as possible without frequent occurrence of hypoglycemia. A goal would be an HbA1c of 7.0%.

The primary responsibility for diabetes management will be with the treating or referring physician, but additional support of the research team including a Certified Diabetes Educator (CDE) will be made available.

Participants will be expected to take a sufficient number of daily insulin injections or use insulin pump therapy to meet this goal, without causing severe hypoglycemic reactions. In general, glucose levels must be checked at least four times per day and records of the glucose levels should be communicated to the CDE every two weeks. After the CDE has reviewed these records, the CDE may contact the participant and the treating physician about adjustments in the insulin regimen, referral to a Registered Dietician, or other approaches that the CDE feels would improve the glucose control. Records of glucose logs and communication with the participant and treating physician will be kept as source documentation.

The general goal of glucose control is to target pre-prandial glucose levels of 90-130 mg/dl (5-7.2 mmol/L) (plasma), post-prandial levels of <180 mg/dl (<10 mmol/L), and bedtime levels of 110-150mg/dl (6.1-8.3 mmol/L). Participants who fail to achieve an HbA1c level according to the guidelines above will not be excluded from the study, but additional measures will be instituted to correct the glycemic control. The intent is not to eliminate a participant who is trying their best to achieve these aims.

In addition to Medical Monitor and DSMB oversight, regular monitoring of HbA1c levels will be done by the TrialNet Clinical Monitoring Group. Members of this group will work with clinical sites to review diabetes care for individual participants not attaining the study goal.

Any episodes of severe hypoglycemia (i.e. unconsciousness, seizure, or needing assistance of another individual to correct the hypoglycemia due to an altered state of consciousness) will prompt a review of the cause of the episode and adjustment

of insulin dosing/diet/exercise as deemed appropriate by the treating physician. All episodes of severe hypoglycemia that require hospitalization and/or emergency care will be reviewed by the TrialNet Medical Monitor and reported to the Data Safety Monitoring Board (DSMB). If adhering to these goals of treatment results in any episodes of severe hypoglycemia, the goals of treatment may be relaxed to avoid a recurrent event. This will be decided on a case-by-case basis with recommendations of the DSMB and/or other monitoring committees as appropriate (Safety Monitoring Committee, Clinic Monitoring Committee).

6.2.8 EBV PCR Monitoring (Visits -1 for all & Visits 1,2,3,4,5,6,7,8,9,10,11,12,13,15 for Participants who are Seronegative at Screening)

Definition: EBV/PCR Viral Load in whole blood is associated with immunosuppression. This test is used as a tool to monitor participants who have not had a past EBV infection.

Those who have a positive EBV/PCR result at screening (result is ≥ 100) will be excluded from participation in this study. Those who have a positive EBV IGM antibody will be excluded from participation in this study.

For participants who are EBV/PCR negative (result is ≤ 99) with a positive EBV IGG antibody (Seropositive), EBV PCR monitoring is not required after screening.

For participants who are EBV/PCR negative (results is ≤ 99) with a negative EBV IGG antibody (Seronegative), EBV PCR monitoring is required after screening for the baseline visit through visit 6, visits 7 through 13, and visit 15.

If a subject who is seronegative at screening has an EBV PCR result that is ≥ 100 for a EBVPCR done at subsequent visits post screening, injections must stop until EBV PCR results indicate copies/mL are ≤ 99.

If a subject who is seropositive at screening is tested for EBV PCR infection (whether by accident or at the request of the site PI or sub-investigator) and has a result ≥ 2000 copies/mL, injections must stop until EBV PCR results indicate copies/mL are ≤ 1999. The medical monitor and principal investigator must confirm that participant may restart treatment before injections are restarted.

If the subject becomes positive, confirmation testing will be done and study medication withheld until absence of signs and symptoms of infection including negative viral load. This will be assessed by follow-up assessments with appropriate clinical tests including EBV serology at 2, 4, 8, 12 weeks, and then monthly. For participants whose EBV/PCR results post screening is equal to 100-500 please contact the TNCC for direction.

Upon resolution of infection (result ≤ 99) please contact the TNCC to confirm that the participant may restart injections. For participants whose EBV/PCR results post screening are equal to 100-500 please contact the TNCC for direction.

*****IMPORTANT NOTE:** The medical monitor has requested that viral monitoring continue for those subjects with active infections (EBVPCR+) at subsequent visits (visits 16-19) in long term follow up until resolution.

6.2.9 Immunizations (Flu Vaccination – Visit 3 until visit 12 inclusive & Tetanus Vaccination – Visit 12)

Immunizations Overview

Immunization with live vaccine and concurrent use of live vaccines within 3 months of canakinumab therapy is contraindicated during the canakinumab study as the possibility exists for canakinumab to affect host defenses against infections putting a subject at increased risk of infection. Subjects who enter the canakinumab study must be at least one month from their last live vaccination to be eligible for the canakinumab study. With all other vaccines there is a concern that canakinumab may reduce the efficiency of the immunization. Thus, participants should receive anticipated routine immunization before study admission or upon completion of the study. Exceptions to this include the killed flu vaccine and tetanus vaccine which will be given as part of the study (the killed flu vaccine will be given as part of the study while on

treatment only). Subjects who choose to abstain from receiving vaccinations are eligible to participate in the trial but must be counseled about the potential increased risk of infection. Below is the recommended vaccination schedule for US children and adults.

Immunization	recommended age	Notes
Hepatitis B	birth, 2 m, 6m	Series can be started at any age for those not immunized
DTaP: Diphtheria, tetanus, and acellular pertussis	2m, 4m, 6m, 18m, 5y	
Tdap: Tetanus, diphtheria, and pertussis booster	11-12y	
Td: Tetanus, diphtheria	every 10 years	starting after a Tdap dose
Hib: Haemophilus influenzae type b	2m, 4m, 6m, 15m	(not relevant to current study)
IPV: Inactivated poliovirus vaccine	2m, 4m, 6m, 5y	IPV is acceptable
PCV: Pneumococcal conjugate vaccine	2m, 4m, 6m, 15m	(not relevant to current study)
Rota: Rotavirus vaccine	2m, 4m, 6m	live vaccine--contraindicated in TrialNet during study (not relevant to current study)
killed influenza (injection, not flumist – affective against A/H1N1, influenza A/H3N2, and influenza B)	every fall	starting age 6m, 2 doses the first time if under 9y
MMR: Measles, mumps, and rubella (German measles)	12-15m, 5y	live vaccine--contraindicated in TrialNet during study
Varicella (chickenpox) vaccine	12-15m, 5y	live vaccine--contraindicated in TrialNet during study
Hep A: Hepatitis A vaccine	12-24m	2 shots at least 6 months apart (given to unimmunized older children and adults prior to some international travel)
HPV: Human papillomavirus (HPV) vaccine	11y	3 shots over 6 months age 11-26, boys and girls
MCV: Meningitis vaccine		to be given by college entrance
Miscellaneous: Yellow fever, typhoid (oral only, IM polysaccharide vaccine is OK), smallpox including household contacts, BCG and zoster	Not part of usual immunization schedule but sometimes recommended for international travel or for immigrants	All contraindicated

Killed flu vaccine immunization (also known as inactivated influenza vaccine)

At visit 3 (month 2) up until visit 12 (month 11) inclusive, subjects will receive their annual clinically indicated killed flu vaccine at the appropriate time of the year. Response to these immunizations will be determined through analysis of pre- and 4 weeks (+/- 7 days) post-dose samples.

October or November is the best time to get vaccinated, but you can still get vaccinated in December and later. Flu season can begin as early as October and last as late as May. The flu season may differ for international sites.
The killed flu vaccine shots are given subcutaneously, in the arm. Different side effects can be associated with the flu shot. Some minor side effects that could occur are

- Soreness, redness, or swelling where the shot was given
- Fever (low grade)
- Muscle aches
- Headache
- Fatigue
- Chills

If these problems occur, they begin soon after the shot and usually last only a few days. Almost all people who receive influenza vaccine have no serious problems from it. However, on rare occasions, flu vaccination can cause serious problems, such as severe allergic reactions. **The 2010-2011 vaccine provides protection again A/H1N1 (pandemic) influenza, influenza A/H3N2, and influenza B. It will not prevent illness caused by other viruses.**

IMPORTANT: Long Term Follow Up – For visits 16-19 sites will no longer be provided with the killed flu vaccine, however we encourage participants to continue to get vaccinated annually. Please remember per the inclusion criteria that participants must wait 3 months following their last dose of Canakinumab/placebo before they may receive live vaccines.

Tetanus Immunization

The participants in this study will have had a previous series of tetanus shots as part of normal medical care. Subjects who are 18 months or more from their previous tetanus immunization will receive a tetanus immunization at visit 12.

At visit 12, the participants will have a pre-immunization blood draw and then receive a tetanus immunization with follow-up blood draw assessing immune response at visit 13. A Pharmacy Vaccine Request Form is provided in the Protocol Management Home and on page 42 of the Pharmacy Manual..

The shot is given intramuscularly. There may be pain and soreness at the site of the injection and possibly a low-grade fever that could develop 24 to 72 hours after the immunization. These could be treated with anti-pyretics and mild analgesics (e.g. acetaminophen and aspirin).

Emergency Vaccination

If a subject requires an emergency vaccination of any type, the site staff should be alerted as soon as possible.

For the tetanus, if a subject receives the vaccination outside of the study, the post-vaccination tetanus serology should be drawn at the next study visit that is at least 30 days from the date of the vaccination and the site should work with the TNCC to identify a pre-vaccination tetanus serology sample.

6.3 Clinical Assessments

6.3.1 Screening Medical History (Visit -1)

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 guide

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

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

6.3.2 Interim Medical History (All visits except screening visit)

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

Procedure:

Step 1. Utilize source document as guide

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

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

6.3.3 Routine Physical Exam (Visits -1, 1, 4, 7, 10, 13-19)

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 guide

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

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

6.3.4 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 conmeds need to be captured on source documents and the e-CRF.

For TN14 in particular, all subjects using warfarin will be excluded from the study so are providing sites with a list of CYP450 substrates and ask that all medications used by subjects be checked against this list to determine whether use is appropriate. If there is such use, we will request that frequent and close therapeutic monitoring (by assessment of either biomarkers [coagulation factors] or drug levels if a biomarker is not available) of individuals concomitantly treated with agents that are substrates for CYP450. We do note, however, that this is a theoretical concern as to date there is no evidence (not only for canakinumab, but also for other monoclonal antibodies) to suggest that the in vitro findings would translate into any clinically significant effect. See section 13 for list of cytochrome P450 Substrates.

Procedure:

Step 1. Utilize source document as guide

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

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

6.3.5 Participant and/or Parent Survey (Visit 4, 13 & End of Study - prior to debriefing visit)

Definition: a survey to obtain prospective information about the participant's feelings and attitudes pertaining to specific aspects of study participation.

All participants and/or parents (guardians) will be asked to complete the questionnaire.

- Participants will still be allowed to participate in the study even if they choose not to participant in this aspect of the study

Completed by participant and/or parent (guardian):

- The survey is written at a 5th grade level.
- Participants age 10 or older should complete the participant survey.
- Parents should also complete the parent survey if the participants are less than 18 years old.

Completed Anonymously

- Answers will not be shared with the participant's local TrialNet Study Team
- Coordinator should make every effort to receive only sealed questionnaires from the participant/parent/guardian

Procedure

Questionnaires will be processed by the TNCC as Teleforms.

- Teleform versions of the participant/parent/guardian surveys will be made available online.
- There will be links to each survey on the Participant Details Page that the sites can use to print the Teleforms for that participant only.
    - Participant ID and Local ID will be pre-populated.

1 Coordinators should provide the blank teleform surveys to participant/parent/guardian who consent to participate.

2 Coordinators should review the Teleform Information and Instructions sheet with the participant/parent/guardian.

3 Coordinators should ensure the Participant IDs are correct on each page of the teleform BEFORE the participant/parent/guardian begins the survey.

4 The envelope needed for participant/parent/guardian to enclose and seal completed surveys should also be provided before the participant/parent/guardian begins the survey.

5 Coordinators will not be able to assist the participant/parent/guardian with completing any answers on the surveys.

6 Instruct participant/parent/guardian to complete all of the questions to the best of their ability.

- Encourage participant/parent/guardian not to leave any questions blank
- Participant/parent/guardian does not have to answer any questions that may make them uncomfortable.
- Participant Directions and Teleform Information and Instructions sheets may be given to the participant/parent/guardian for assistance while they complete the survey if needed*. *if IRB approved

7 Completed teleform surveys should be placed in the appropriate envelope and sealed by the participant/parent/guardian.

- Coordinators should make every effort to receive only sealed questionnaires from the participant/parent/guardian.

8 Site coordinator should immediately forward sealed envelope via FedEx to the TNCC for processing.

Mailing Procedures

Coordinators may consider sending the Participant/Parent/Guardian Survey by mail to participant that have gone off treatment and may not be in the clinic for visits post baseline.

- Every effort should be made to ensure:

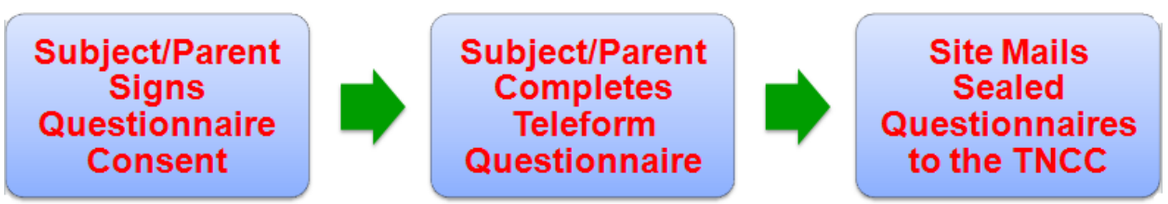
- Subject/parents understand how to complete the Teleform surveys off-site.
- Completed surveys are sealed and returned from the subject/parent's residence to the study site PRIOR to being sent to the TNCC.

Coordinators should mail the following:

- Teleform Information and Instructions (if IRB approved)
- Parent/Participant/Guardian Surveys Directions (if IRB approved)
- A copy of the applicable, blank Teleform survey for the participant/parent/guardian who has agreed to participate. For those who opt out of participation in either the initial, follow-up, or final survey we ask that you complete the tracking form.
  - Ensure all pages of the blank teleform survey have been included.
  - Ensure the Participant IDs are correct on each page of the teleform BEFORE mailing.
- The envelope needed for participants/parents/guardians to enclose and seal completed surveys.
- A postage-paid return envelope addressed to the site.

Completed teleform surveys should be placed in the appropriate envelope and sealed by the participant/parent/guardian.

- Participant/parent/guardian should then place the sealed envelope in the postage-paid return envelope addressed to the site and mail.
  - Coordinators should make every effort to receive only sealed questionnaires from subjects/parents via mail.
- Site coordinator should immediately forward sealed envelope with questionnaire via FedEx to the TNCC for processing.



6.4 Tests and Assays

6.4.1 PPD Test (Visit -1)

Definition: The PPD is a special skin test for tuberculosis (TB). It is a test used to determine if someone has developed an immune response to the bacterium that causes tuberculosis (TB). This test should be performed whenever TB is suspected. It is at the discretion of the site study investigators how frequently this test is required.

Supplies Needed:
Alcohol cotton swab
¼ to ½ inch, 27-guage needle
Tuberculin syringe gauge

Procedure
Step 1. Administration of PPD Test
a. Utilize sterile technique

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

Step 2. Results of PPD
a. The results of the PPD test need to be read within 48-72 hours of administering the test.
b. The test must be read by a trained nurse or physician (either at the study site or at a site more convenient for the participant).
c. The results of the test should be recorded in the participant's source documents.
d. It may be helpful to call the participant as a reminder to have the test read in a timely manner and to call the site with the results.

6.4.2 Urine Pregnancy Test for Females with Childbearing Potential (All visits except visit 6A)

Definition: The urine pregnancy test is to determine if a female is pregnant or not.

Supplies Needed:
Cup to collect urine sample
Pregnancy Dipping Stick

Procedure:
Step 1. Collect Urine Sample
Have participant urinate in cup

Step 2. Reading Results
a. Receive urine sample
b. Follow directions provided with pregnancy test.

6.4.3 MMTT (Mixed Meal Tolerance Test) (Visit -1, 2, 4, 6A, 7, 8, 10, 13-19)

Definitions: MMTT is commonly used in the U.S. It is a liquid meal (Sustacal/Boost High Protein) that is ingested in the fasting state with timed measurements. Also this test is meant to assess the potential participant's insulin production capability. This assessment will be conducted at least 3 weeks (21 days) from diagnosis of diabetes and within one month (37 days) of randomization. In order for the results to be meaningful, it is important for the participant to follow certain dietary and lifestyle guidelines in the days preceding the test. A high carbohydrate diet must be followed for the three days leading up to the test.

* The test should be **rescheduled** if the participant has a blood glucose (measured on his/her home meter) **less than 70 mg/dl (3.85 mmol/L) or greater than 200 mg/dl**. **(11.1 mmol/L)**

The participant is required to fast starting the night before the test, and is instructed to consume only water for at least ten hours preceding the test. More detailed information on the mixed meal tolerance test can be found in Appendix A. This appendix includes detailed information on the procedure. This section also includes a detailed "Sample Menu" with recommended items to maintain the required high carbohydrate diet prior to the test.

There are 2 types of MMTT(s) for the TN14 study:
a. 4-hour MMTT (Visits -1, 13, and 15)
Note: During visit -1, 13, and 15, if the participant is < 12 years of age at time of screening , then a 2-hour MMTT will be done.
b. 2-hour MMTT (Visits 2, 4, 6A, 7, 10, 14, 16-19)
Note: Done for all participants

Mixed Meal Dose: The test meal (Boost High Protein) is given at a dose of 6 mL per kilogram body weight. Maximum dose is 360 mL. Boost High Protein is supplied in 8 fluid ounce containers.

The MMTT takes approximately four hours to complete, and must be scheduled in the morning (i.e. must be started before 10 AM). It is important to carefully review the eligibility criteria with the participant before starting the test, since if certain criteria have been violated the test will need to be rescheduled for another date. For participants that live a great distance from the clinic, special arrangements to have the MMTT done the same day as the initial Screening Visit would be attempted if a second trip to the clinic would not be possible.

Time Measurements: Record all times using the 24-hour clock format, using the key below:

12-Hour Clock	24-Hour Clock
1:00 am	01:00
2:00 am	02:00
3:00 am	03:00
4:00 am	04:00
5:00 am	05:00
6:00 am	06:00
7:00 am	07:00
8:00 am	08:00
9:00 am	09:00
10:00 am	10:00
11:00 am	11:00
12:00 pm (noon)	12:00

12-Hour Clock	24-Hour Clock
1:00 pm	13:00
2:00 pm	14:00
3:00 pm	15:00
4:00 pm	16:00
5:00 pm	17:00
6:00 pm	18:00
7:00 pm	19:00
8:00 pm	20:00
9:00 pm	21:00
10:00 pm	22:00
11:00 pm	23:00
12:00 am (midnight)	00:00* (next day)

Dosing: Below is a Dosing calculation as to the amount of Boost High Protein to be given to the participant:

DOSE CALCULATION WORKSHEET

BOOST Dose:

- 6 mL/kg up to a maximum of 360 mL.

BOOST High Protein Dose Given:

_____**mLs**
(BOOST High Protein dose in mL)

BOOST High Protein bottles contain 8 fluid-ounces (240 mL) *Please read label to ensure correct Boost is administered **BOOST High Protein**

BOOST High Protein **Dose Calculation**
Subject's weight in pounds_____ multiply by 0.454 = _____kg
Subject's weight in kg _____ multiply by 6 = _____ mL of BOOST High Protein
(not to exceed 360 mL)

Example: a person weighing 110 pounds weighs 110 lbs x 0.454 = 49.9 kg and requires a dose of BOOST High Protein 49.9 kg x 6 = 299.4 mL (about one and one-four bottles)

Procedure: Mixed Meal Dose

Step 1. Ensure the subject is currently fasting

Step 2. Prepping Participant for MMTT

a. The MMTT must begin between 7:00 - 10:00 a.m. for proper interpretation.
b. Obtain the weight of the participant and calculate Boost High Protein meal size = 6 mL/kg, up to 360 mL, 1lb = 0.45 kg

c. The MMTT test uses a standard oral mixed meal formula (Boost High Protein®, Mead Johnson Nutritional Division, Evansville, Indiana) composed of liquid sucrose, soy protein, casein, and soy oil. The test meal is given at a dose of 6 kcal/kg body weight, at 1 kcal/mL to a maximum of 360 kcal.
d. The participant should remain sitting or resting in bed quietly throughout the test.

Note: The participant can engage in quiet, non-strenuous activities such as reading, playing cards, watching TV and may walk to the bathroom between blood draws if necessary (but should otherwise remain in resting position until the test is completed). It is recommended that participants not be asked to answer questions for the purpose of completing case report forms during the MMTT.

e. Place an I.V. line into an antecubital vein, using an intracatheter/butterfly needle (usually 20 or 22 gauge depending upon the size of the participant). *Note: The intracatheter may be kept patent between samples with a slow saline drip or heparinized saline solution (as per the guidelines of your institution) in a 20 mL syringe, injecting about 2-3 mL after each blood draw.*
f. Before the procedure, fill several 3 mL syringes with luer-lock tips with 1 mL normal saline solution to flush the adapter after each blood draw. This is only necessary if the blood sampling is more than 3 minutes apart.

Step 3. Obtain baseline samples:

a. The first sample should be taken at least 10 minutes after establishing the line(s) and when participant is calm and relaxed (if possible, depending on age) - this is the "-10 minute" sample
b. The second sample should be taken just prior to drinking the Boost High Protein - this is the "0 minute" sample
c. Meal consumption - Start the clock at the beginning of the drink. The dose of Boost High Protein must be completely consumed within five (5) minutes.
d. Obtain post-meal blood samples.
e. Samples are taken at 15, 30, 60, 90, and 120 min after time 0' (if this is a 4-hour test, samples should also be taken at 150, 180, 210 and 240 minutes)
f. A timer should be turned on at 0 min
g. The actual start time for each blood draw should be recorded on the MMTT specimen transmittal form

Sampling Protocol:

Time (min)	**Glucose Sample Collected 1.2 mL gray top tube**	**C-peptide Sample Collected 1.2 mL lavender top EDTA tube**
-10	X	X
0	X	X
Drink Boost High Protein		
15	X	X
30	X	X
60	X	X
90	X	X
120	X	X
150†	X	X
180†	X	X
210†	X	X
240†	X	X

† Samples only taken at the these times during a 4-hour MMTT

h. If a clogged line, missed sample, or other deviations from the protocol occur, these must be noted on the "Comments" section of the MMTT specimen transmittal form.
i. Termination of MMTT
    i. Test is terminated after the blood sample at 120 minutes for a 2-hour MMTT, or 240 minutes for a 4-hour MMTT. At that time, the indwelling cannula(e) will be withdrawn, pressure applied and a sterile strip bandage applied.

j. Upon completion of the test, the participant should have a snack, for example peanut butter or cheese crackers, coffee, milk or ginger ale.

MMTT Administration Eligibility ☑ Checklist**

☐	Subject fasted (did not eat) after 10:00pm the night before the test up until the start of the test *__Includes:__ *Subject avoided all food, drink (EXCEPTION: water)*
☐	Followed allowable insulin guidelines: • Long-acting insulin can be administered the day before the test is scheduled. • Corrective insulin (Humalog (H) and NovoLog) can be administered up to two hours before the test. • Regular (R) insulin can be administered up to six hours before the test. • Participants on insulin pumps (continuous insulin infusions (CSII)) should continue with the normal basal rate, but a Humalog (H) or NovoLog bolus may be added up to 2 hours prior to the test, and Regular (R) bolus up to 6 hours prior to the test.
☐	Subject abstained from consuming *coffee, tea, sodas, caffeine containing drinks, cigarettes, alcohol, or chewing gum* during the fasting period (10 hours before the test)
☐	Subject refrained from vigorous exercise during the fasting period (10 hours before the test).
☐	Subject refrained from working during the night preceding the morning of the test.
☐	PI reviewed medication list including over the counter meds to determine whether ok to proceed with test. Note, PI may contact TNCC CRA, Study Chair, or TN Vice-Chair if he/she is uncertain about whether MMTT should be performed.
☐	If subject has had an illness, surgery, or infection the PI has evaluated the subject and determined whether the test should be done. Note, the PI may contact the TNCC CRA, Study Chair, or TN Vice-Chair if he/she is uncertain about whether the MMTT should be performed
☐	Subject ate a high carbohydrate diet (at least 150 grams) (*Sample Menu* - see Appendix A, Section 13, pg 150 of the MOO for details) for 3 days prior to testing.
☐	If subject has had an illness, surgery, or infection the PI has evaluated the subject and contacted the TNCC CRA, Study Chair, and Dr. Carla Greenbaum to determine whether test should be done
☐	Subject is not pregnant, does not have any chronic illness such as cancer, nephritic syndrome, active hepatitis, or some other life threatening illness.
☐	At the start of MMTT the subject's blood glucose was greater than or equal to 70 mg/dl but less than or equal to 200 mg/dl (between 70 mg/dl – 200 mg/dl)
☐	MMTT started after 7AM or before 10 AM (i.e. -10 min sample was drawn after 7AM or before 10AM)

***If any items are not checked (including "not applicable" where appropriate) or you have questions or concerns please contact your protocol CRA at the TNCC before you move forward.*

6.4.4 Link to Sample Collection, Processing, & Shipping Procedures (Non-Mechanistic Samples)

Autoantibodies (Visit -1)	TrialNet Autoantibodies BAA ICA Collection Shipping 28SEP2010.pdf
Chemistries (Visit -1, 7, and 13)	TrialNet Chemistries Collection Shipping 28SEP2010.pdf *****Instructions Specific to TN14 Anti IL-1Beta due to Fructosamine Testing*****
EBV & CMV Serology (Visit -1)	TrialNet EBV CMV Serology Collection Shipping 28SEP2010.pdf
EBV/PCR (Visit -1 for all Subjects & Visits 1-6, 7-13, 15 for Seronegative Subjects Only)	TrialNet EBVPCR CMVPCR Collection Shipping 28SEP2010.pdf
Flu Serology (Killed flu administered during study from visit 3 until visit 12 inclusive)	TrialNet Flu Serology Collection Shipping 28SEP2010.pdf
HbA1c (Visit 1, 4, 7, 10, 13-19)	TrialNet HbA1c Collection Shipping 28SEP2010.pdf
HIV, Hep B & C (Visit -1)	TrialNet HIV HepBC Collection Shipping 28SEP2010.pdf
HLA Determination (Visit 1)	TrialNet HLA-DNA Collection Shipping 28SEP2010.pdf
MMTT (Mixed Meal Tolerance Test) (Visit -1, 2, 6A, 7, 8, 10, 13-19)	TrialNet MMTT Collection Shipping 28SEP2010.pdf
Tetanus Serology (Visit 12)	TrialNet Tetanus Serology Collection Shipping 28SEP2010.pdf

6.4.5 Link to Mechanistic Sample Collection, Processing, & Shipping Procedures

Serum for Cytokines (Visit 1, 4, 6, 7, 10, 13-19)	TrialNet Cytokines Collection Shipping 28SEP2010.pdf
Serum for Immunogenicity (Visit 1, 4, 6, 7, 10, 13-19)	TrialNet Immunogenicity Collection Shipping 28SEP2010.pdf
Mechanistic Serum (Visit -1 and 6 ONLY)	TrialNet Mechanistic Serum Collection Shipping Visit -1 and 6 ONLY 28SEP2010.pdf
Mechanistic Serum (Visit 1, 4, 7, 10, 13-19)	TrialNet Mechanistic Serum Collection Shipping Other Visits 28SEP2010.pdf
PK(Pharmacokinetics)/**Cytokines** (Visit 1, 2, 3, 4, 6, 13, 14)	TrialNet PKCytokine Collection Shipping 28SEP2010.pdf
Whole blood – Plasma/PBMC (Visit, -1 ONLY)	TrialNet PBMC PLASMA Collection Shipping Screening Visit ONLY 09NOV2010.pdf
Whole blood – Plasma/PBMC (Visit, 1, 7, 13, 15)	TrialNet PBMC PLASMA Collection Shipping Other Visits 09NOV2010.pdf
Whole blood – RNA (Visit 1, 4, 7, 13, 15)	TrialNet RNA Collection Shipping 28SEP2010.pdf

TrialNet Specimen Handling Summaries 28SEP2010.pdf

For details beyond collection and shipping procedures please refer to the current lab manuals.

6.4.6 CBC (Complete Blood Count) with Differential (Visit -1, 7, and 13)

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.

Supplies Needed:

Supply	Collection /Shipment
1 x 2 mL EDTA lavender top tube	Collection/Shipment
Alcohol Proof Pen	Collection

Procedure:

Step 1. Collect CBC Specimen
a. Label one 2 mL EDTA lavender top tube with the specimen type (CBC w/Diff).
b. Draw the 2mL blood into 2 mL EDTA lavender top tube (or equivalent) according to the instructions provided by your local lab.
c. Process the sample according to the instructions provided by your local lab

Step 2. Complete e-CRF specimen collection form. For abnormal values please specify if they are clinically significant or not.

6.4.15 Sample Destruction

Procedure for the Destruction of Participant Samples

If a participant determines that they do not want their samples stored, whether during enrollment or the course of the study, the TrialNet Coordinating Center (TNCC) is responsible for notifying the laboratories of the participant's request and ensuring it has been successfully completed. Upon notification of samples destruction, the laboratories will destroy any participant samples in storage and no further samples from that individual will be saved.

This procedure details the necessary steps for sample destruction:

1. A written request must be submitted to the TNCC Laboratory Coordinator, Page Dunning (Fax: 813- 910-1229) or Page.Dunning@epi.usf.edu by the clinical site and signed by the site Principal Investigator. The following should be specifically addressed in the request:
   - Participant ID Number (no subject names or identifiers)
   - TNCC Study Name
   - Laboratory and Assay(s)
   - Circumstances/ Reason for sample(s) destruction
   - Subject Request (Reason for: Withdrawal or requested sample(s) destruction, Other)
   - Laboratory Request (Reason: Sample not labeled, Other)
   - Date of Request

2. The Laboratory Coordinator will review the request, initiate and coordinate the destruction of samples with Core Laboratories/Repositories, as appropriate. This will be done via a Sample Destruction Form/Log that will document the request and the date(s) the sample(s) are destroyed. This will be maintained on file at the TNCC by the Laboratory Coordinator and at the respective Core Laboratories/Repositories.
3. The Laboratory Coordinator will send a notification in writing to the site Principal Investigator confirming that the requested sample(s) have been destroyed per the subject's request.
4. Sample data/results obtained prior to the date of the subject request will be maintained in the database for the purpose of analysis, but all sample results generated after the request date will not be recorded in to the TNCC database or used for analysis purposes.
5. All sample destruction information will be recorded at the TNCC.

6.5 Subject Transfer – Permanent Transfer

Note: sites are not required to exchange source documentation. This practice is not prohibited, but sites are required to adhere to their institutional policies when transferring medical documentation.

Instructions for the originating site, new site, or temporary site are available in the Pharmacy Manual for TN14 Anti IL-1Beta

6.5.1 Originating Site Procedures

If a subject 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 as this will require a notification to the labs and the reimbursement personnel (so an effective date will be required)

Step 2. Determine the most suitable new site for the participant. This can be done by navigating to the member director and search for clinical centers by zip code or by viewing the participating site list at the beginning of this document

Step 3. 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 subject is (time-point) in the study. You CANNOT provide any PHI to the new site until after the subject signs consent/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 subject has not completed the course of treatment. The originating site should contact the TNCC for additional steps regarding transfer of study agent if required.

Step 7. Once all data has been entered/reconciled and the subject has signed the new site's informed consent forms, the originating site should navigate to the PRN form "Permanent Participant Site Transfer" and transfer the subject to the new site. See section 9.6 for instructions on how to access PRN forms.

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

6.5.2 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 to the participant for their review.

Step 3. If the participant wishes to continue participation at the new site, bring the subject to the new site to sign the consent forms.

Step 4. The new site should notify the originating site when the subject has signed the consent forms.

Step 5. The originating site will notify the new site when participant has been transferred in the online system.

6.6 Subject Transfer – Temporary

6.6.1 Originating Site Procedures

If a subject needs to temporarily 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 director and search for clinical centers by zip code or by viewing the participating site list at the beginning of this document. Please contact the TNCC to make sure that this site has IRB approval for the TN14 IL-1Beta study.

Step 3. 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 subject is (time-point) in the study. You CANNOT provide any PHI to the new site until after the subject signs consent/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 subject 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 subject has signed the new (or temporary) site's informed consent forms, the originating site should navigate to the PRN form "Permanent Participant Site Transfer" and transfer the subject to the temporary site. See section 9.6 for instructions on how to access PRN forms. Once this form has been completed the originating site will no longer have access to the participant's details.

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

6.6.2 Temporary Site Procedures

Step 6. 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 7. Once the participant has made contact, schedule the participant for a visit or mail the temporary site consent forms to the participant for their review.

Step 8. If the participant wishes to continue participation at the temporary site, bring the subject to the temporary site to sign the consent forms before performing any study procedures.

Step 9. The temporary site should notify the originating site when the subject has signed the consent forms.

Step 10. The originating site will notify the temporary site when the participant has been transferred in the online system.

Step 11. When the participant has completed the course of study planned at the temporary site, the temporary site will contact the originating site and will ensure all e-CRF(s) have been completed for the visits conducted at the temporary site before completing another PRN form "Permanent Participant Site Transfer" which will transfer the participant back to the originating site.

6.7 Pregnancy

Pregnant and lactating women will not be enrolled in the study. All females of reproductive age (Tanner Stage 3+) must have a negative pregnancy test prior to enrolling in the study and will be required to avoid pregnancy and requested to use two acceptable birth control (or abstinence) for the first 15 months of the study. At every study treatment visit the sexual activity of female participants of reproductive age will be re-assessed. If a subject who was previously sexually inactive becomes sexually active or tanner stage increases, she will be counseled about the need to use two reliable forms of birth control (or abstinence). Pregnancy tests will also be completed at all follow-up visits and any pregnant women will not undergo MMTTs. Currently there is no human data on the effects of this drug on the fetus.

Once a participant is randomized, if they become pregnant, the participant will not have any further study drug injections or MMTT(s) until the end of their pregnancy. Whether the participant carries the pregnancy to term or terminates the pregnancy early the participant will be allowed to restart MMTT(s) and study drug injections post pregnancy as appropriate within the time windows for the study. If the participant decides to breastfeed, they may move forward with having subsequent MMTT(s), but will not be able to restart study drug injections until breast feeding is discontinued.

If a subject 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

Step 3. If the study visit in which the subject is found to be pregnant is a study drug administration visit, **DO NOT** administer study drug.

Step 4. If the study visit in which the subject is found to be pregnant requires an MMTT, **DO NOT** conduct an MMTT

Step 5. Complete the “Pregnancy Confirmation” e-CRF PRN form. See section 9.6 for instructions on how to access PRN forms

Step 6. Ask the participant if they would be willing to be followed on the study and allow the study to record information about their pregnancy outcome.

a. If the participant does not want to be followed or withdraws consent complete the “Change in Status” form. See section 9.6 for instructions on how to access PRN forms
b. 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. See section 9.6 for instructions on how to access PRN forms.
    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 7. Place a note to file in the subject 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 8. Fulfill any local reporting requirements (IRB, GCRC, ect)

Step 9. Notify TNCC of any concerns or questions and if and when the participant gives birth.

*****IMPORTANT:** For **SAFETY**, we don't want pregnancy until after 3 mths of drug (i.e. 15 mths). For **EFFICACY** (i.e. 2 year MMTT) we don't want pregnancy through the 2 year endpoint.

7. Informed Consent Process

7.1 Overview

7.1.1 Administration

Each participant will be given a written consent form by qualified study personnel (the Trial Coordinator and/or Investigator or other designee). The personnel will understand the research study, and will complete any necessary courses required by their Institutional Review Board prior to implementing the consent process. The consent process should occur in a quiet setting, and the participant should be given time to review the written consent form and ask questions prior to the initiation of study procedures. This ensures that the participant understands that participation is voluntary and that they may choose to end participation at any time. The consent form will be reviewed with participants and signed **prior** to performing any study-related assessments. It should also be noted in the participant's medical/research chart that the participant consented to participation in the study and the site's consenting process should be filed either in the participant's binder or trial regulatory binder.

Participants under 18 years of age will be given the opportunity to discuss the study and consent form independently from their parent or guardian, which will allow these participants to ask questions they might not have felt comfortable asking previously. In addition, the parent/guardian of the adolescent participants will be given the opportunity to discuss the study independently from the participant. One or both parents/legal guardians (depending on institutional policies) will be required to sign the Informed Consent Forms. At some sites, the participant will also be required to sign an Assent Form. Care should be taken to explain the study to the participant on a level that is understandable. Specific questions should be addressed to the participant to help ensure that the study is completely understood.

Study personnel must provide the participant's family with:

- An overview of the full study
- The inclusion and exclusion criteria
- Information on the procedures involved
- A description of the potential visits
- Required time commitments for participating in the study

The participant's signature should be obtained on the Informed Consent Form/Assent Form after a thorough discussion of the study.

Provide a copy of the consent form(s) to the participant/family after the form is signed. Sites may also provide a copy of the consent form to the participant/family prior to signature if the participant/family wishes to leave and review the form(s) in order to consider participating on the study. The site may also mail a copy of the consent form(s) to potential participants.

The **consent form/assent form(s) MUST be signed at the participating site** in full view of a delegated/appropriate study staff member. The consenting process must take place before any study procedures are conducted. An assessment tool is available *to document the consenting process – See section 14.4 Assessment Tool.* ***Please note that this assessment tool titled** "Documentation of Enrollment_Consent Process" is also located online in the TN14 Protocol Area, folder entitled "*TN14 – (C): Forms"

7.1.2 HIPPA Authorization/Other Forms

An explanation of the Health Insurance Portability and Accountability Act (HIPAA) should also be included as part of this discussion regardless of whether or not an institution has incorporated the Research Subject Authorization Form (RSAF) into the Informed Consent Forms. It is also a legal requirement that the participant receive a copy of their signed RSAF (if required), regardless of whether or not the authorization is a separate form or is incorporated into the Informed Consent Forms.

7.1.3 Consent Retention

A copy of the signed Informed Consent and Research Subject Authorization Form (if in the United States) should be provided to the participant. **The original signed documents should remain at the clinical site**. These original and

signed documents should **not** be sent to the TrialNet Coordinating center. Each site must retain original consent documents for no less than 7 years after study final closure at the site.

***Please file a copy of your consenting process in each of your participants' charts.**

7.1.4 Completion of All Required Areas

All signature, date, checkboxes, and initial lines must be completed by the participant, participant's representative or guardian, witness, trial coordinator, and investigator where applicable. The person obtaining consent should sign and date the same day as the participant or the participant's representative/guardian/witness. Please ensure that the printed areas are completed legibly.

7.1.5 Consent Revisions

Informed consent obtained at a clinical site should follow all standard procedures. The participant must sign a revised IRB approved I*nformed Consent Form* with each revision of the document.

7.2 Consent for Participants 18 years or older

Forms to use:

- Screening Consent- to be signed by the participant and others (witness, investigator, trial coordinator) as applicable
- Interventional Consent- to be signed by the participant and others (witness, investigator, trial coordinator) as applicable
  - Ensure the **Optional MMTT** section is completed by the participant (check boxes and subject initials)

7.3 Consent for Participants 17 and younger

Sufficient evidence must be provided to show that the person giving consent for the minor does, in fact, have the legal right to serve as the participant's guardian. The parent/guardian must sign and date the form as well as print his/her name legibly. One or two parental signatures will be required as per the requirements of the local institution

- Screening Consent- to be signed by the participant's guardian/representative in accordance with local IRB approval and others (witness, investigator, trial coordinator) as applicable. It may be that some IRB's will require both parents of a child to sign each consent form.
- Screening Assent- to be signed by the child/participant and others (witness, investigator, trial coordinator) as applicable.
- Interventional Consent- to be signed by the participant's guardian/representative in accordance with local IRB approval and others (witness, investigator, trial coordinator) as applicable. It may be that some IRB's will require both parents of a child to sign each consent form.
  - Ensure the **Optional MMTT** section is completed by the participant's guardian/representative (check boxes and subject initials)
- Interventional Assent- to be signed by the child/participant and others (witness, investigator, trial coordinator) as applicable.

*****IMPORTANT: If a participant began the study before the age of 18 and therefore originally signed an assent, they will need to be re-consented on an adult ICF once they reach the age of 18. The reason this is required is because when signing an assent, they are still legally represented by a guardian/parent and cannot give consent to participate without their guardian's signature. Once they turn 18, participants are legally adults and are therefore solely responsible for giving consent for continuing participation in the study.**

7.4 Additional Consent

Additional consent for testing for reportable conditions such as HIV or Hepatitis B or C will be obtained as required by individual institutions. If participants are found to have evidence of HIV or Hepatitis B or C, they will be excluded from the study but referred for appropriate counseling by specialists in these areas according to local regulations.

8. Data Management

a. 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 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 would require that the numbers match to properly identify the participant.

b. Protocol Tool Management

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

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

c. System Requirements

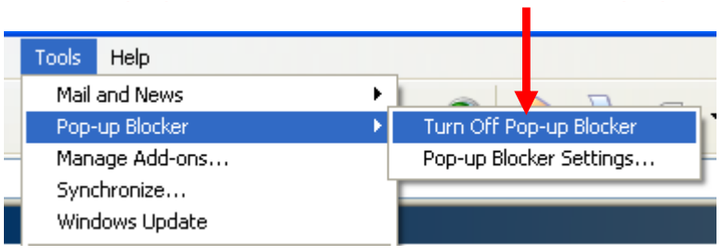
In order to use the web-based Protocol Management Tools system you need to have:
Hardware and software

- 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.
- Please make sure your pop-up blocker is turned off (see snapshot on next page):

Step 1. To do this go to “Tools” in top horizontal navigation toolbar
Step 2. Select “Pop-up Blocker” and then select “Turn Off Pop-up Blocker”



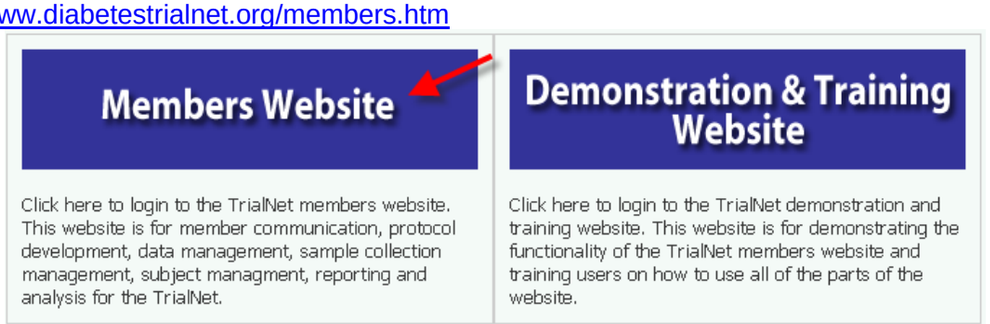
- No intensive training needed to use this application. If you are familiar with the use of a browser you already have the basic knowledge.
- Updates to the system will be done on the server without users disruption
- The system is dependent on the Internet / Intranet for application availability. If 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.

9. Online Data Capture System

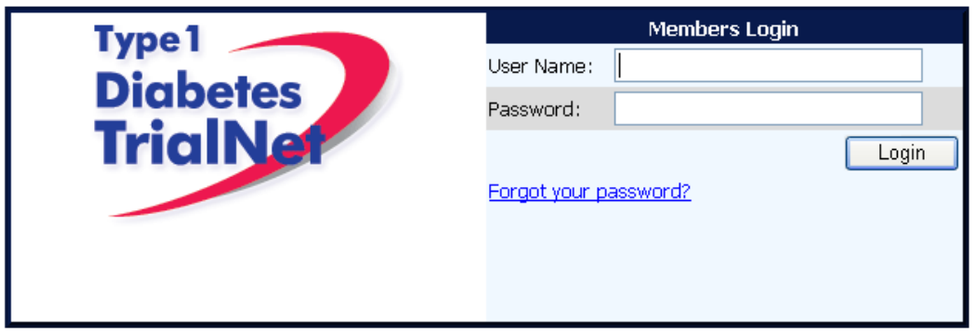
9.1 Overview and Basic Functionality

9.1.1 Login/Navigate to the TN14 Protocol Manager Home Area

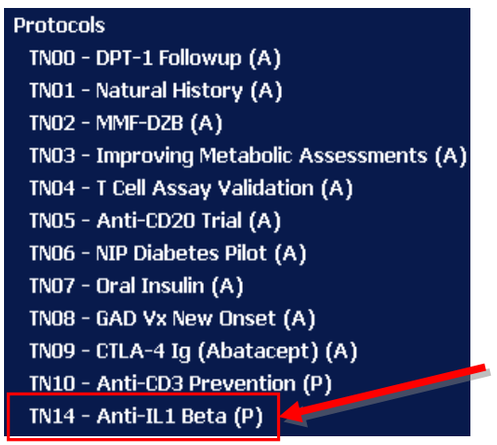
Step 1. Procedure to login and navigate to the TN14 protocol manager home area: Log into TrialNet **Members** Site: http://www.diabetestrialnet.org/members.htm



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



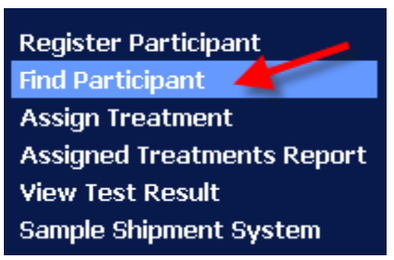
Step 3. Navigate to TN14 Protocol Manager by clicking “TN14 – ANTI IL-1BETA” on the left hand navigation bar



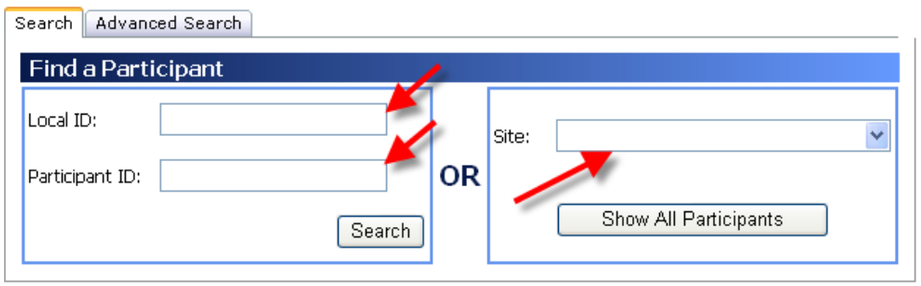
9.1.2 Finding a Participant

Note this procedure will be done for every visit.

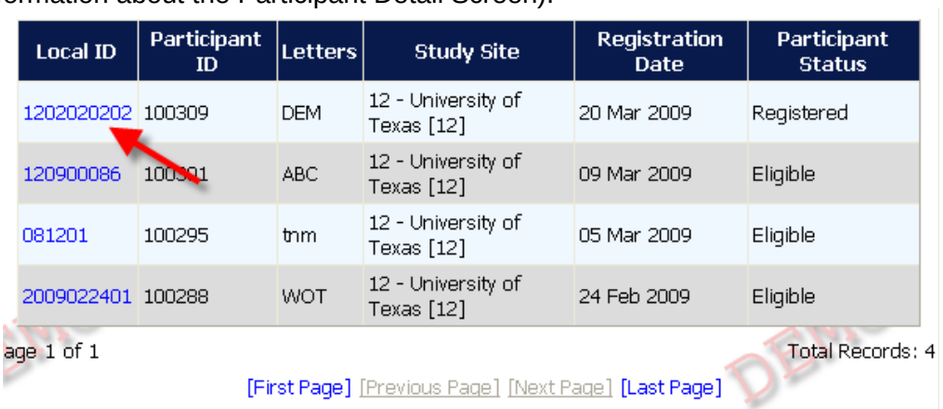
Step 1. Procedure to find participant: Once in TN14 Protocol, navigate to the left hand side and select Find Participant



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



Step 3. The list of subjects matching entered criteria will populate below the search box. Click on Local ID (should be in blue text color). This will open the Participant Detail Screen (see section 9.2 for more information about the Participant Detail Screen).



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

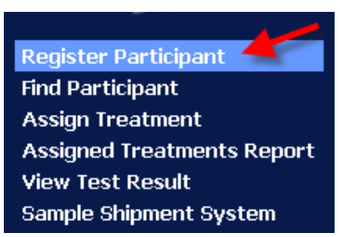
age 1 of 1 Total Records: 4

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

9.1.3 Registering a Participant

Step 1. Procedure Registering a Participant on TN14: Follow Section to Log into TrialNet Members Website and navigate to TN14 protocol manager area (section 9.1.1)

Step 2. Once in TN14 ANTI IL-1BETA New Onset Home Page, from the left navigation menu select Register Participant



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

a. Local ID: Create a Local ID (Please refer to section titled Local ID)

Local ID

- The local site assigns a unique identifier to each participant (Local ID). The TNCC recommends that the Local ID be a nine-character alphanumeric string. The first eight characters will identify the date of screening i.e. YEARMMDD. The last two digit string will be the order of screening i.e. 01. An example of the Local ID is 2009013001.

- However, sites can create their own unique identifier for each participant (local ID), as long as, the local ID can be clearly identified on all items submitted to the TNCC and will serve as verification of the Participant ID.

- It is the responsibility of the local site to maintain a master list of all participants. Participants enrolled on more than one TrialNet protocol should retain the same Participant ID and Local ID number on all protocols

b. Enter First Three Letters of Participant's name

c. Participant ID: Can be skipped if first time participant on TrialNet Study

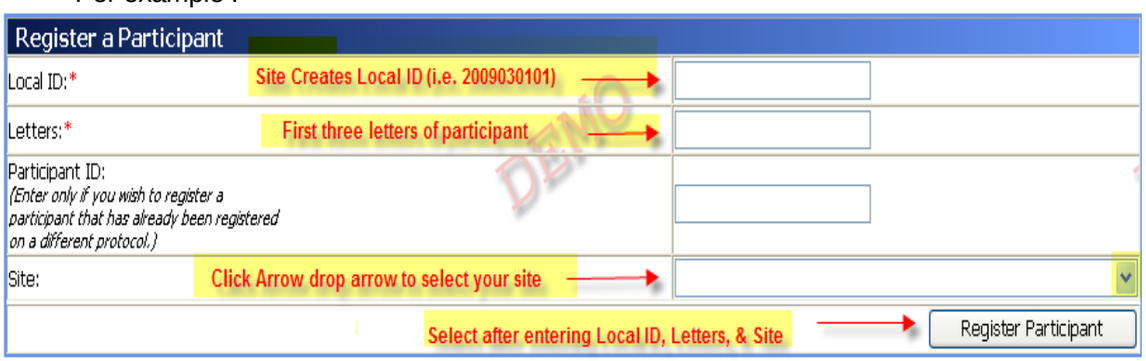
Participant ID

- The Data Management System will assign a unique six-digit participant identification number (Participant ID) for each participant entered in the study. This number should be clearly identified on all forms, specimens and images submitted to the TNCC.

Note: If participant is coming onto this study from another TrialNet Study, then enter the Participant ID.

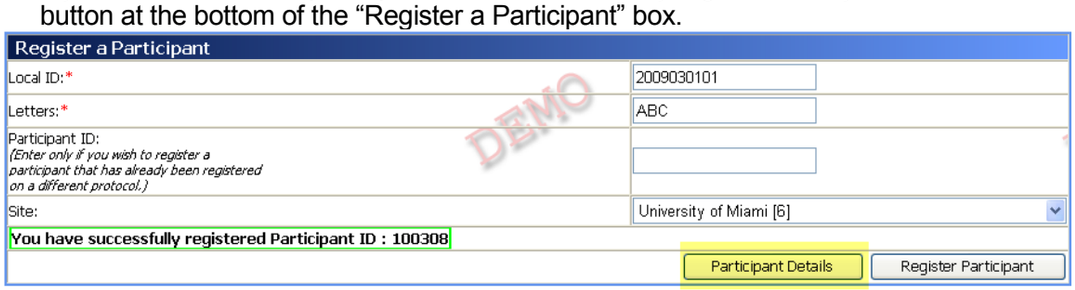
d. Select applicable clinical center

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



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

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

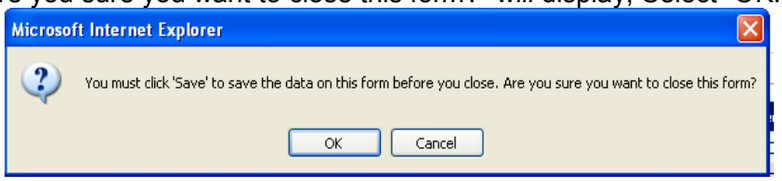


9.1.4 Save and Close e-CRFs

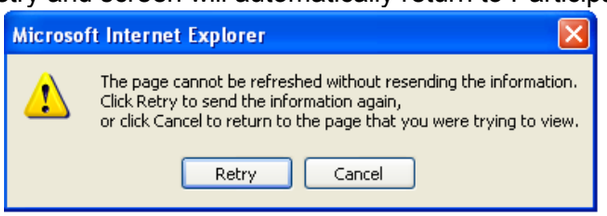
Note: This procedure will be the same after each e-CRF is completed

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

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



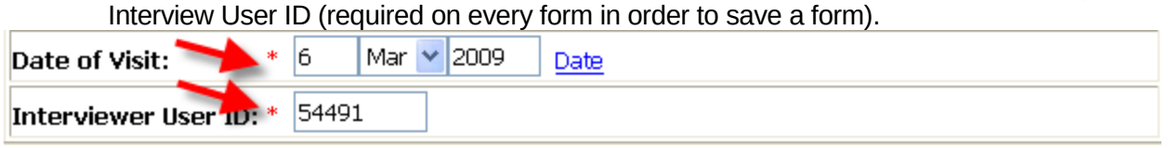
Step 3. The following message will display, “The page cannot be refreshed without resending the information Click Retry to send the information again, or click Cancel to return to the page that you were trying to view.” Select Retry and screen will automatically return to Participant Details



9.1.5 Form Required Fields

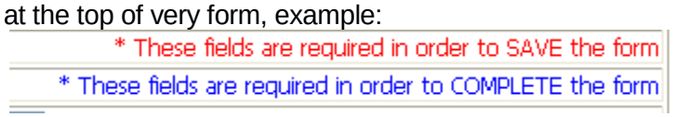
There are two kinds of required fields on every form:

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



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

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

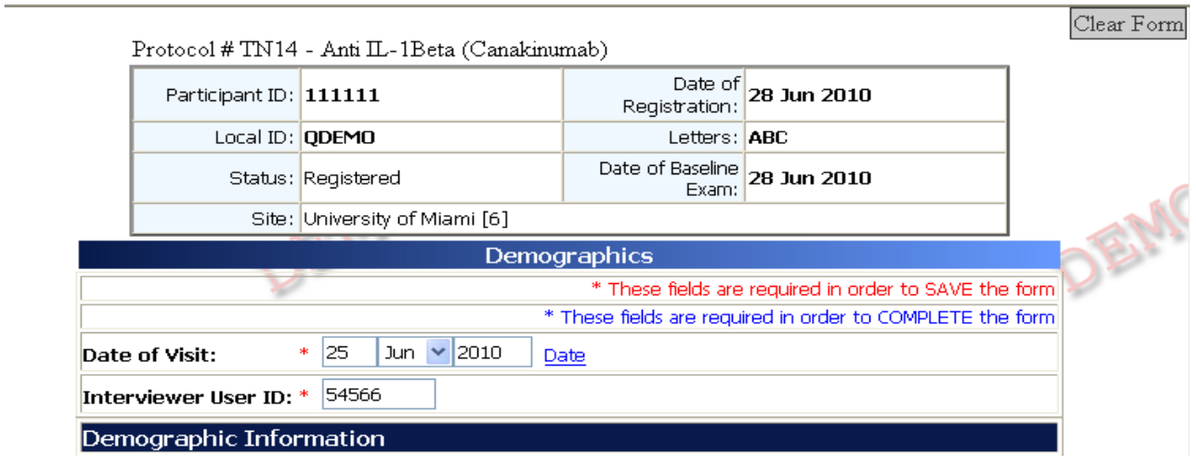


9.1.6 Clear ALL Data from a Form

If you find you have mistakenly entered data on the wrong form or wrong data on a form, you can clear all data on the form as long as you are the person who entered the data on the form.

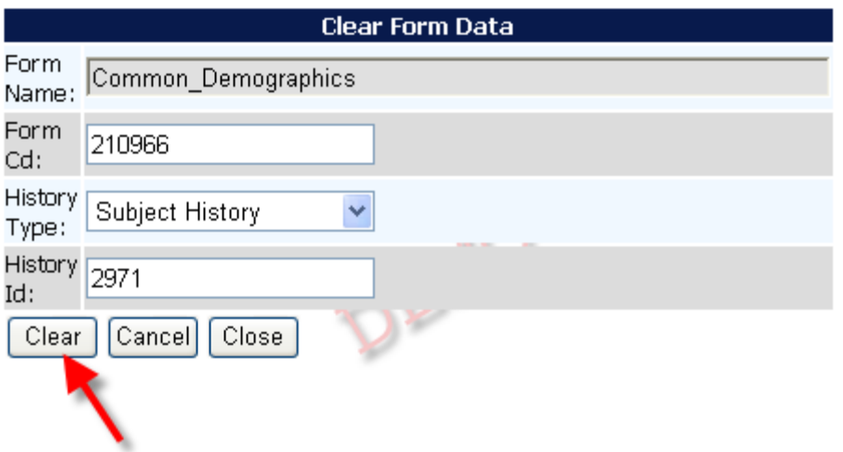
Step 1. Navigate to the form which you would like to clear

Step 2.

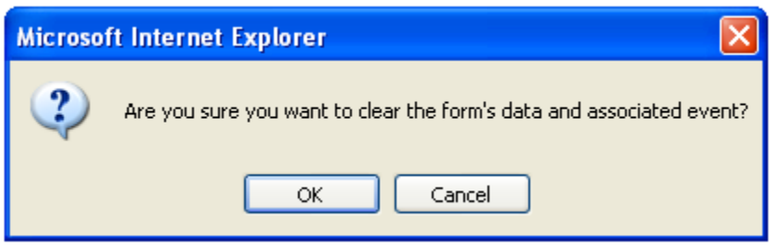


Step 3. Click on the button entitled “Clear Form” in the upper right hand corner of the screen.

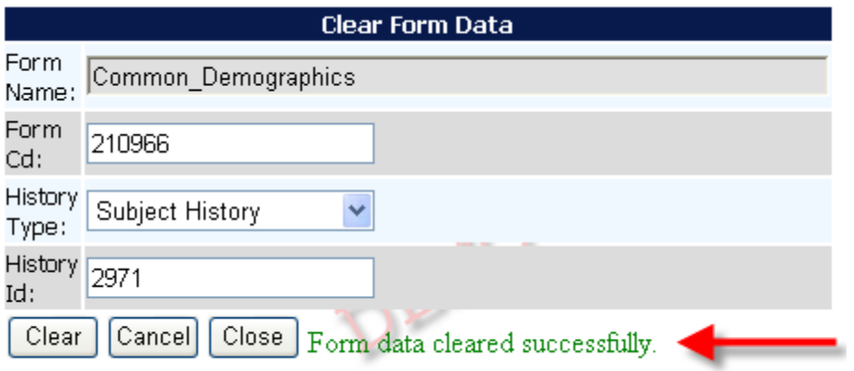
Step 4. The page will navigate to a description of the form you are about the clear (Clear Form Data box). If you are certain you wish to clear out all data on the form, click the button “Clear”



Step 5. A pop-up window will display asking you if you are certain you want to clear the form. If you are certain, click “Ok”



Step 6. You will know the form cleared successfully as green text will appear under the Clear Form Data box.



Step 7. Click the "Close" button and you will navigate back to the participant's details.

9.2 Participant Details

Definition: The Participant Details Screen provides, by participant, a list of all events generally required to be completed once the participant is registered on the study. The forms present at each visit follow the Schedule of Events/Assessments from the protocol. In order to navigate to the participant details follow the instruction provided in section 9.1.2. The following information is provided for each event on the schedule:

- 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)
- 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 red and blue asterisks).
  - If you are unable to **Save** a form then fields on the form with red asterisks which is required data elements are missing

9.3 Screening Visit

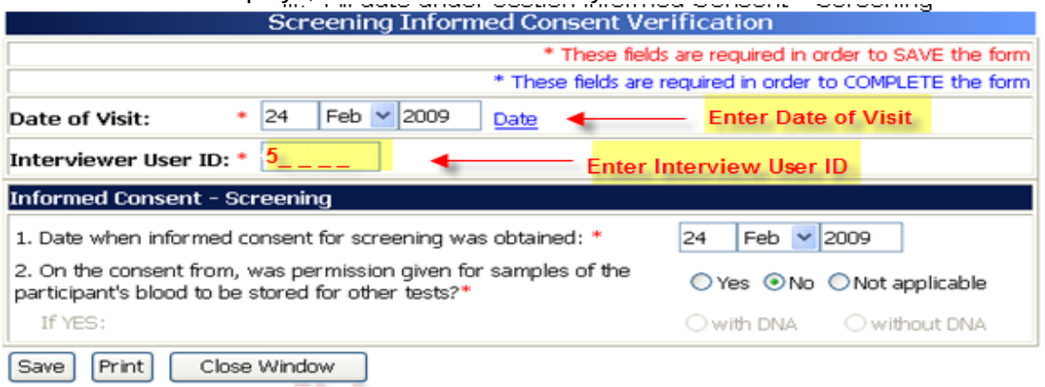
9.3.1 Screening Informed Consent Verification

Step 1. Procedure to enter data for the Screening Informed Consent Verification: Be sure the Source Document is completed prior to completing forms

Step 2. Under Event Title select - Screening Informed Consent Verification

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

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



Step 4. Complete Informed Consent-Screening Section (questions 1 & 2)

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

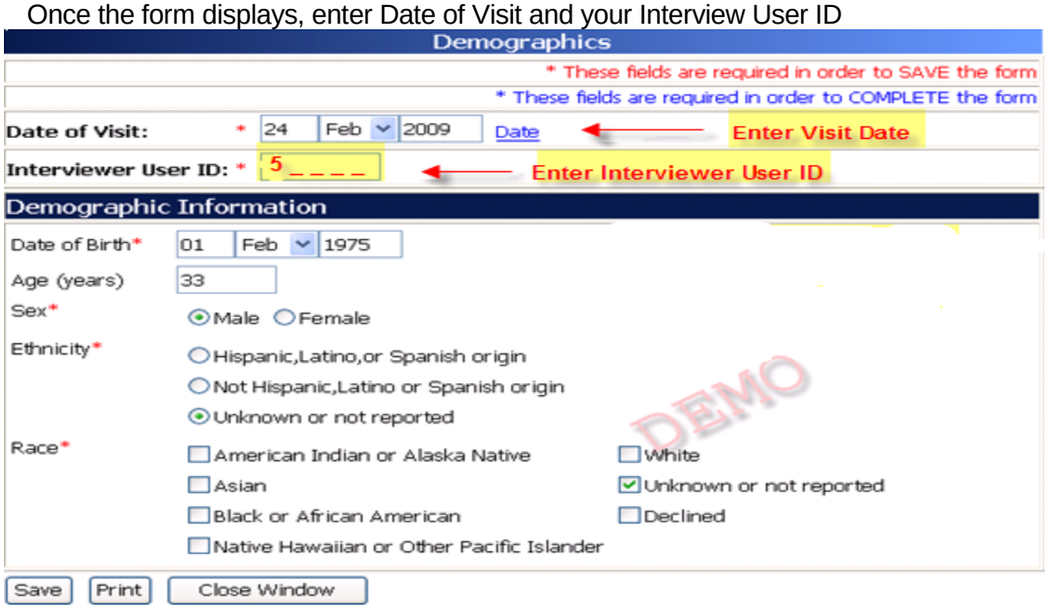
9.3.2 Demographics

Step 1. Procedure to enter data for Demographics: Be sure the Source Document is completed prior to completing forms

Step 2. Under Event Title - Select Demographics

	Demographics	Tracking	02 Mar 2009	18 Mar 2009	Complete

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



Step 4. Complete Demographics Information Section

Step 5. After entering data, please reference section 9.1.4 Save and Close e-CRF form. Please note that this form needs to be completed in order for the MMTT form to populate and be accessible.

9.3.3 Family History

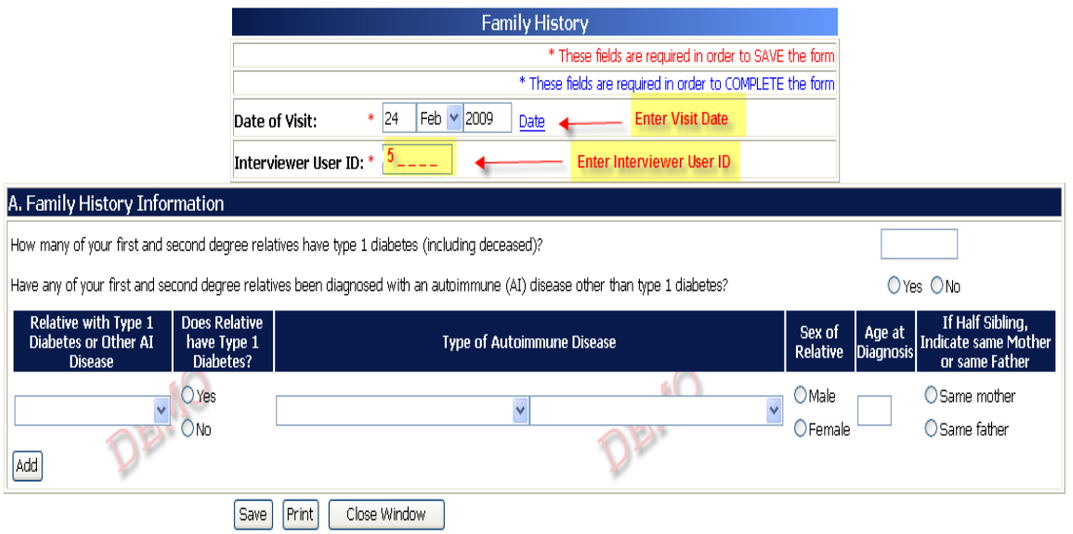
Step 1. Procedure to enter data for Family History: Be sure the Source Document is completed prior to completing forms

Step 2. Under Event Title - Select Family History

Family History	Tracking	02 Mar 2009 - 09 Mar 2009	12 Mar 2009	Complete

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

Step 4. Complete Family History Section



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

9.3.4 Screening Medical History

Step 1. Procedure to enter data for Family History: Be sure the Source Document is completed prior to completing forms

Step 2. Under Event Title - Screening Medical History

Screening Medical History	Tracking	02 Mar 2009	24 Feb 2009	Complete

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

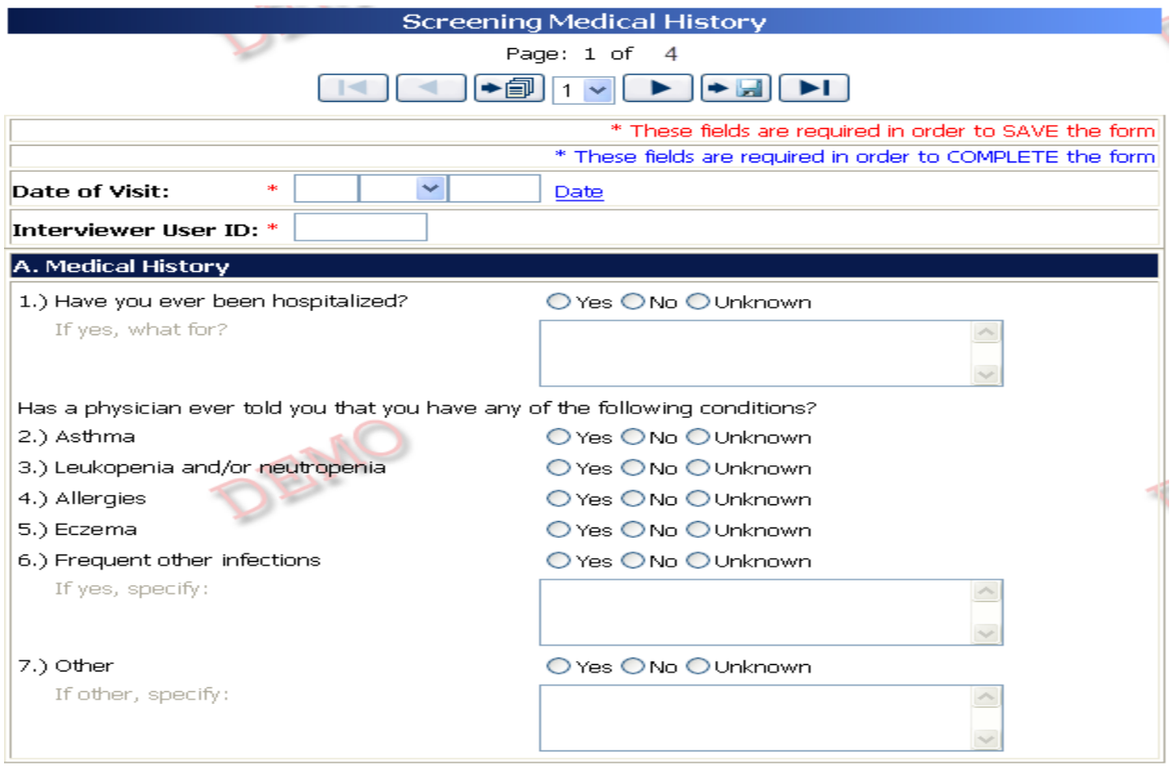
Step 4. Complete all following sections for this form: Note the Screening Medical History Form contains 4 pages.

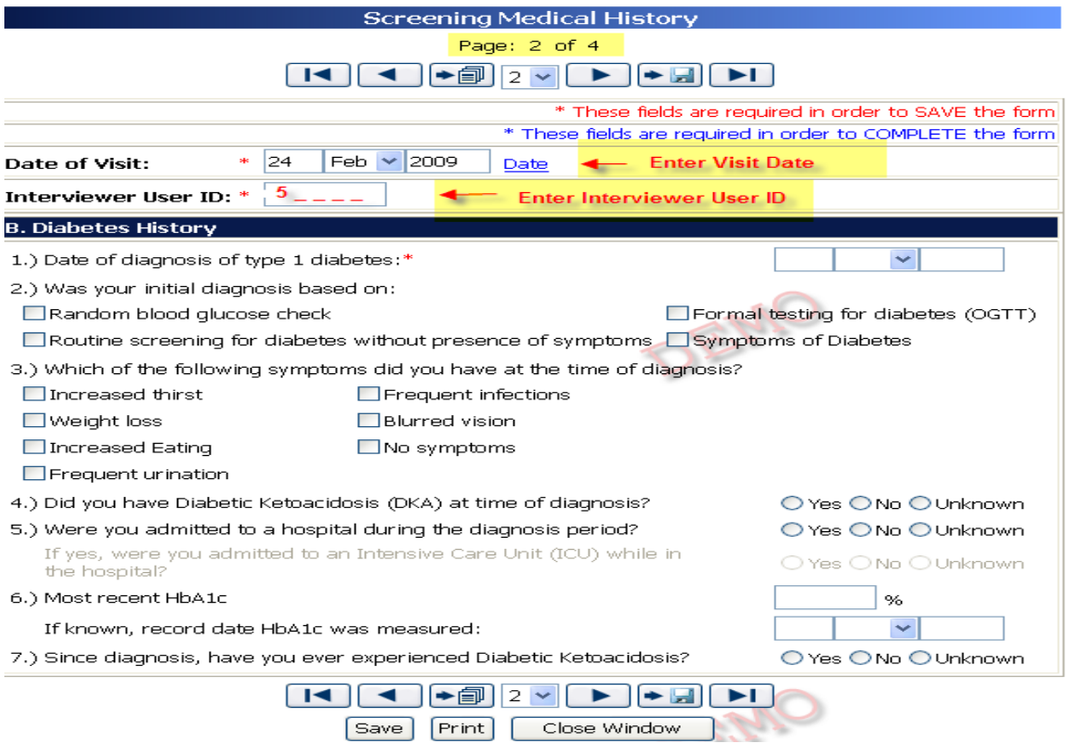
- *a. Section A. Medical History*
  - *1. Review if participant has been hospitalized other then for diabetes*
  - *2. Review of any condition/disease*
- *b. Section B. Diabetes History*
  - *1. Collect information about participant's diabetes history*
  - *2. Section C. Autoimmune Disease History*

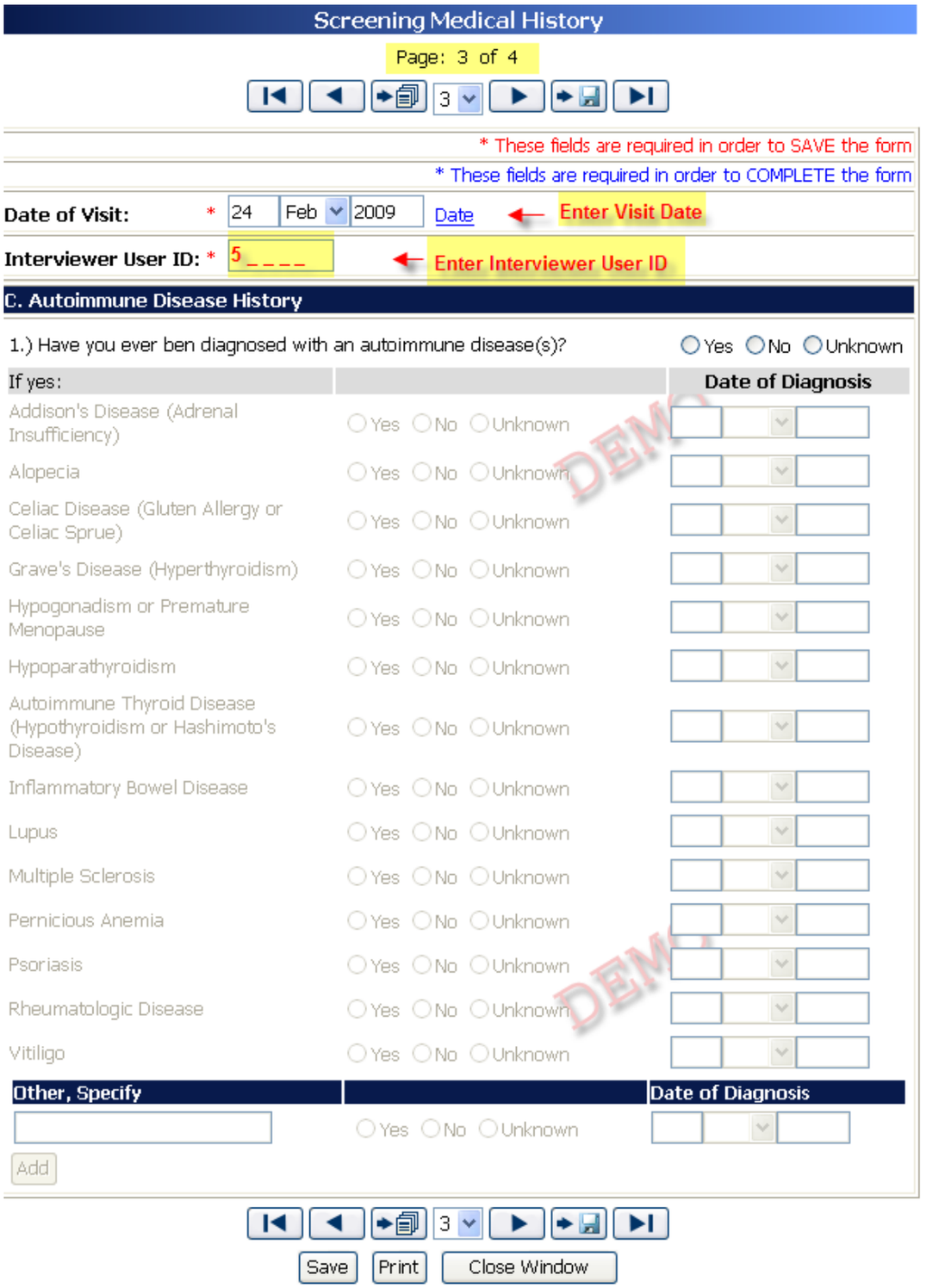
3. *Collect information if participant has an autoimmune disease history*

c. *Section D. Review of Systems*

1. *Collect information of any abnormalities the participant maybe experiencing within his/her system*




Screening Medical History
Page: 2 of 4
2
* These fields are required in order to SAVE the form
* These fields are required in order to COMPLETE the form
Date of Visit: * 24 Feb 2009 Date
Enter Visit Date
Interviewer User ID: * 5
Enter Interviewer User ID
B. Diabetes History
1.) Date of diagnosis of type 1 diabetes: *
2.) Was your initial diagnosis based on:
Random blood glucose check
Formal testing for diabetes (OGTT)
Routine screening for diabetes without presence of symptoms
Symptoms of Diabetes
3.) Which of the following symptoms did you have at the time of diagnosis?
Increased thirst
Frequent infections
Weight loss
Blurred vision
Increased Eating
No symptoms
Frequent urination
4.) Did you have Diabetic Ketoacidosis (DKA) at time of diagnosis? Yes No Unknown
5.) Were you admitted to a hospital during the diagnosis period? Yes No Unknown
If yes, were you admitted to an Intensive Care Unit (ICU) while in the hospital? Yes No Unknown
6.) Most recent HbA1c %
If known, record date HbA1c was measured:
7.) Since diagnosis, have you ever experienced Diabetic Ketoacidosis? Yes No Unknown
2
Save
Print
Close Window
DEMO



Screening Medical History

Page: 3 of 4

3

* These fields are required in order to SAVE the form

* These fields are required in order to COMPLETE the form

Date of Visit: * 24 Feb 2009 Date ← Enter Visit Date

Interviewer User ID: * 5_ _ _ _ ← Enter Interviewer User ID

C. Autoimmune Disease History

1.) Have you ever ben diagnosed with an autoimmune disease(s)? Yes No Unknown

If yes:		Date of Diagnosis
Addison's Disease (Adrenal Insufficiency)	Yes No Unknown	
Alopecia	Yes No Unknown	
Celiac Disease (Gluten Allergy or Celiac Sprue)	Yes No Unknown	
Grave's Disease (Hyperthyroidism)	Yes No Unknown	
Hypogonadism or Premature Menopause	Yes No Unknown	
Hypoparathyroidism	Yes No Unknown	
Autoimmune Thyroid Disease (Hypothyroidism or Hashimoto's Disease)	Yes No Unknown	
Inflammatory Bowel Disease	Yes No Unknown	
Lupus	Yes No Unknown	
Multiple Sclerosis	Yes No Unknown	
Pernicious Anemia	Yes No Unknown	
Psoriasis	Yes No Unknown	
Rheumatologic Disease	Yes No Unknown	
Vitiligo	Yes No Unknown	

Other, Specify		Date of Diagnosis
	Yes No Unknown	

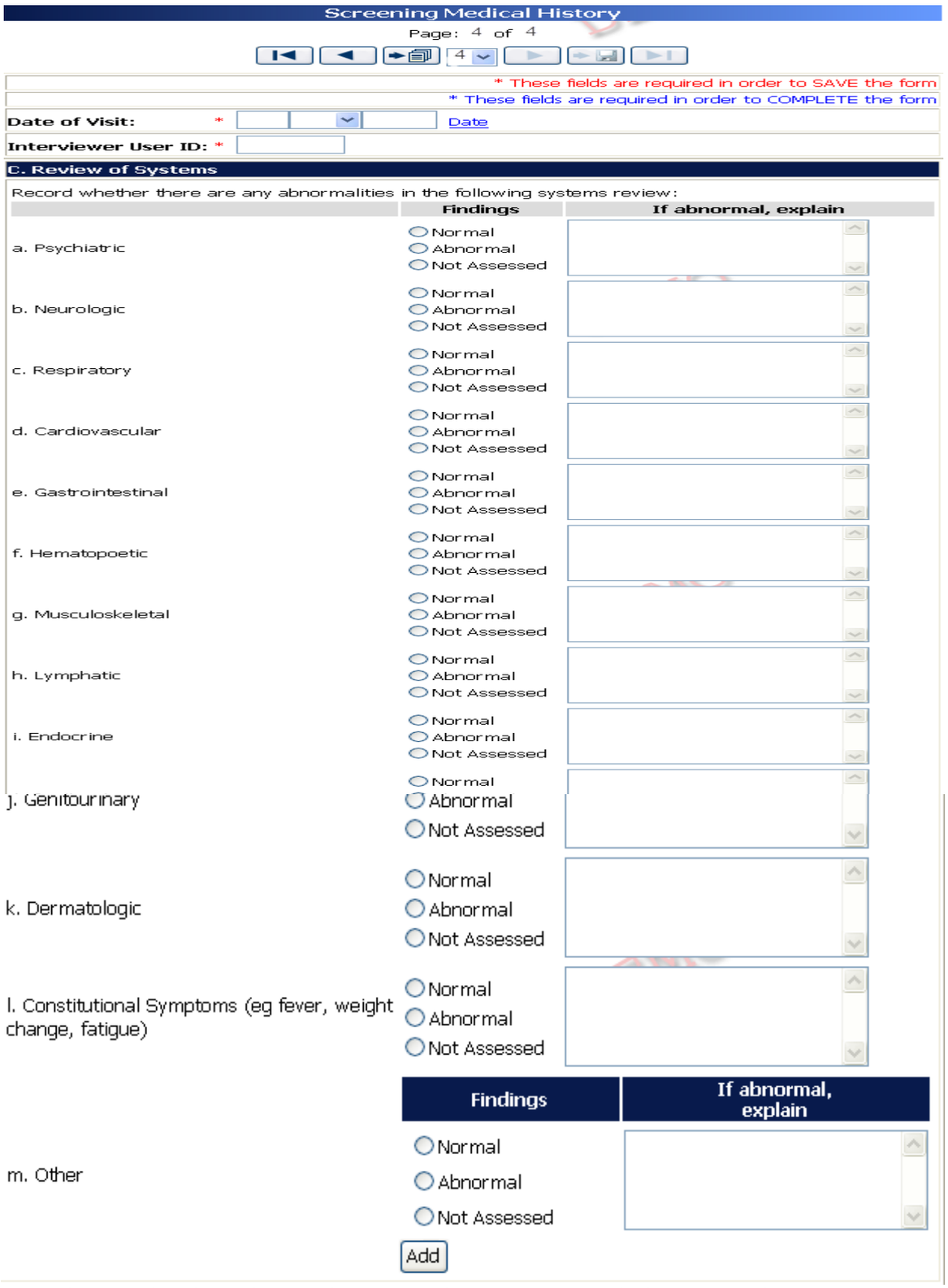
Add

DEMO

DEMO

3

Save Print Close Window



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

9.3.5 Physical Exam

Step 1. Procedure to enter data for Physical Exam: Be sure the Source Document is completed prior to completing forms

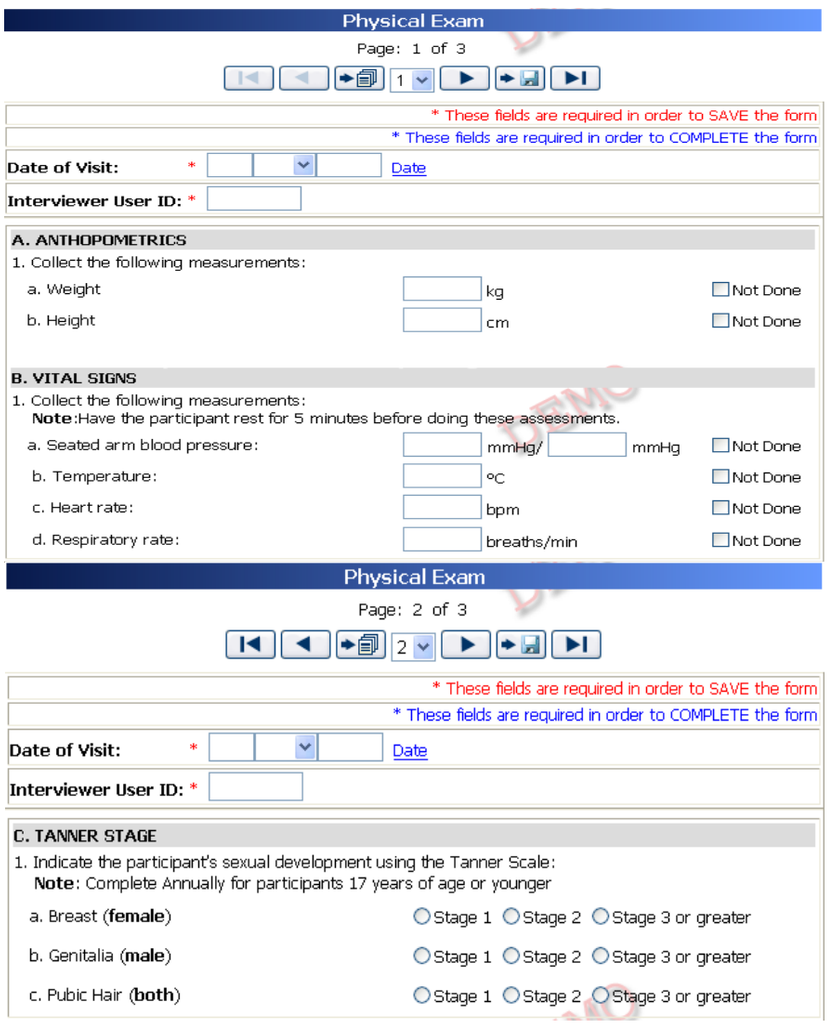
Step 2. Under Event Title - Select Physical Exam

Physical Exam	Tracking	02 Mar 2009 - 09 Mar 2009	24 Feb 2009	Complete

Step 3. When the form displays, enter Date of Visit and your Interview User ID. Complete all following sections for this form:

a. *Section A. Physical Exam*

- *Collect participant's height, weight, and vitals (i.e. blood pressure) and any abnormalities found during the examination.*



Physical Exam

Page: 1 of 3

* These fields are required in order to SAVE the form

* These fields are required in order to COMPLETE the form

Date of Visit: * Date

Interviewer User ID: *

A. ANTHOPOMETRICS

1. Collect the following measurements:

a. Weight kg Not Done

b. Height cm Not Done

B. VITAL SIGNS

1. Collect the following measurements:
Note:Have the participant rest for 5 minutes before doing these assessments.

a. Seated arm blood pressure: mmHg/ mmHg Not Done

b. Temperature: °C Not Done

c. Heart rate: bpm Not Done

d. Respiratory rate: breaths/min Not Done

Physical Exam

Page: 2 of 3

* These fields are required in order to SAVE the form

* These fields are required in order to COMPLETE the form

Date of Visit: * Date

Interviewer User ID: *

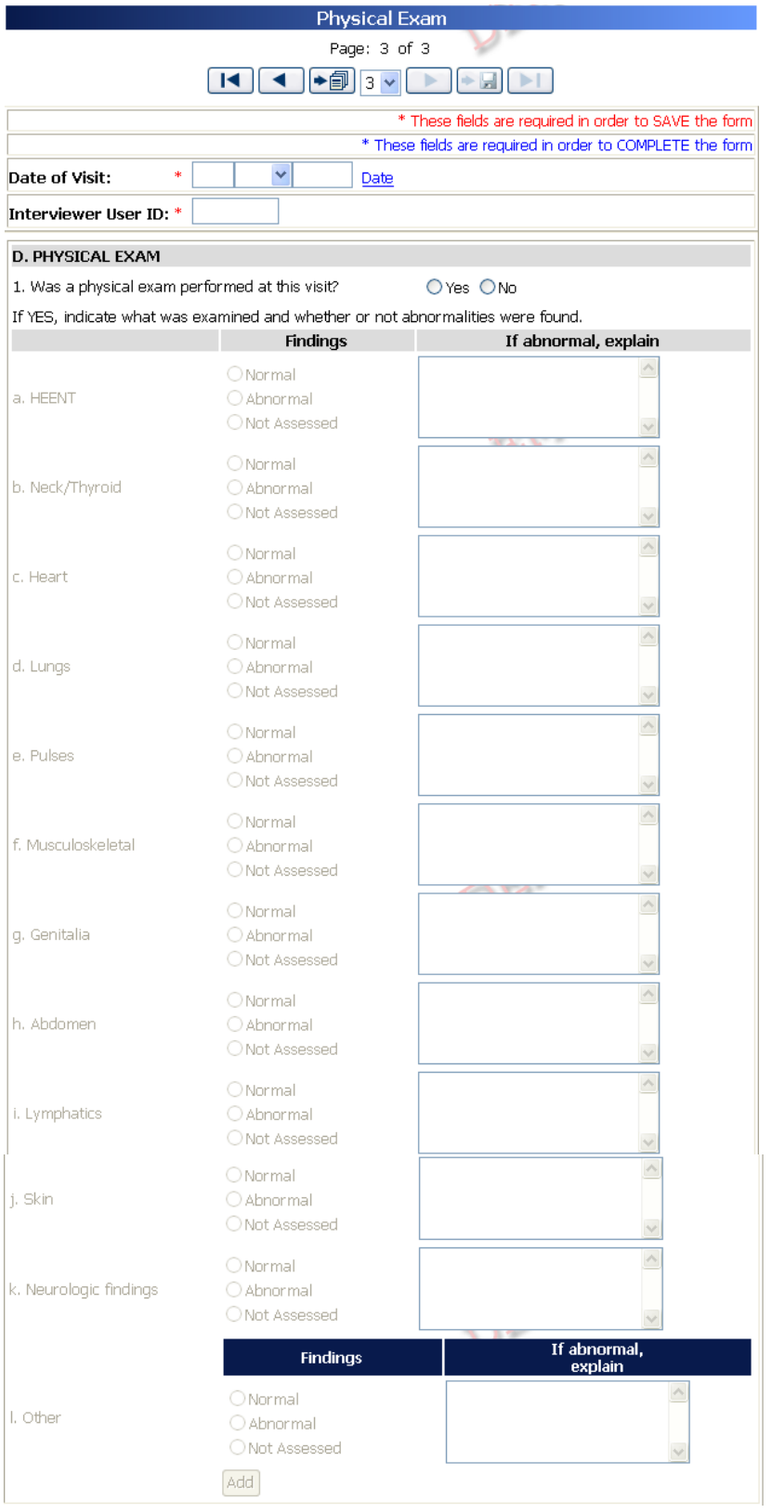
C. TANNER STAGE

1. Indicate the participant's sexual development using the Tanner Scale:
Note: Complete Annually for participants 17 years of age or younger

a. Breast (**female**) Stage 1 Stage 2 Stage 3 or greater

b. Genitalia (**male**) Stage 1 Stage 2 Stage 3 or greater

c. Pubic Hair (**both**) Stage 1 Stage 2 Stage 3 or greater

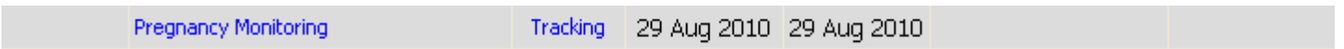


Step 4. After entering data, please reference section 9.1.4 Save and Close e-CRF form.

9.3.6 Pregnancy Monitoring

Step 1. Procedure to enter data for Pregnancy Monitoring (if applicable): Be sure the Source Document is completed prior to completing forms

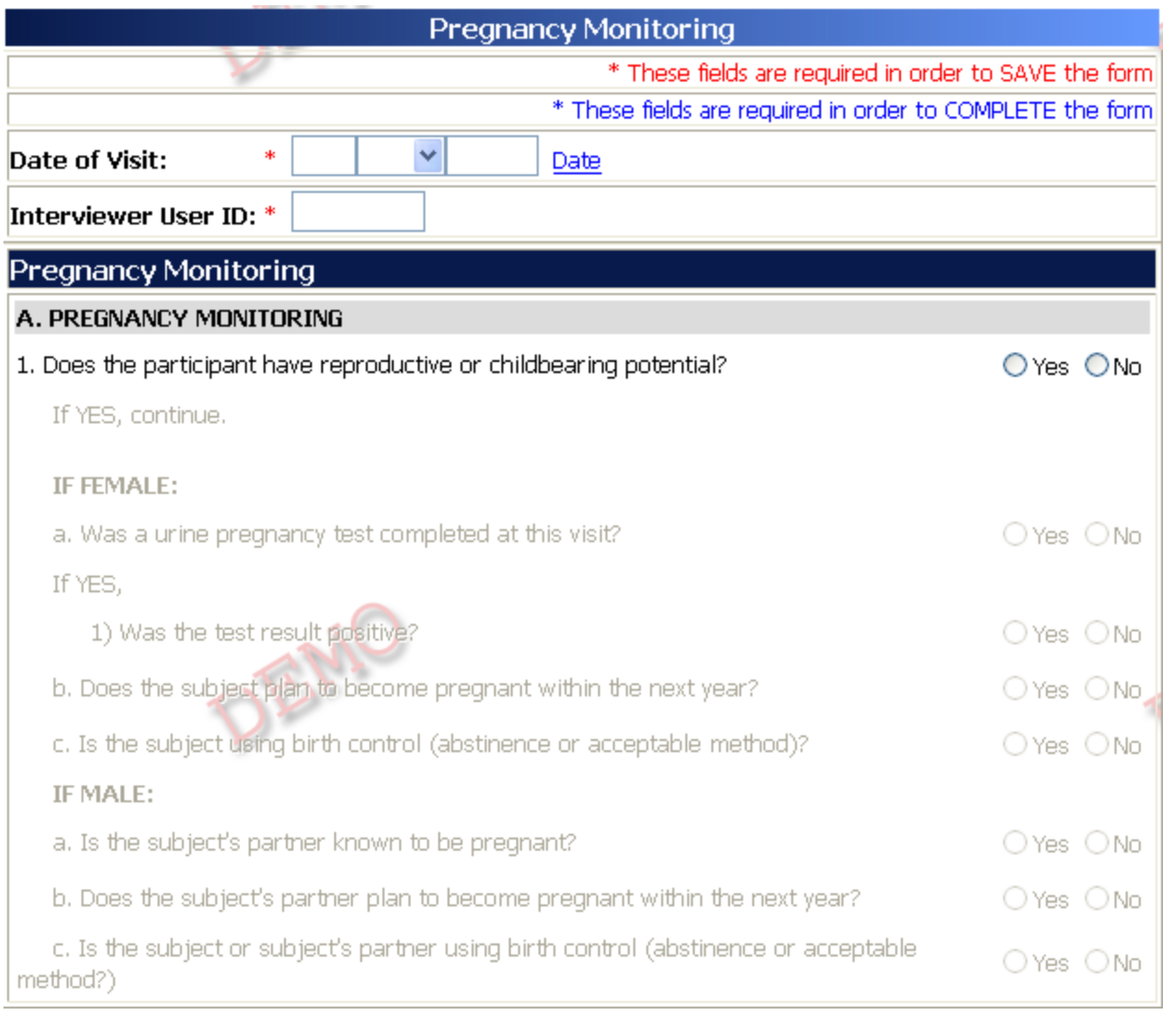
Step 2. Under Event Title - Select Pregnancy Monitoring (if applicable)



Step 3. When the form displays, enter Date of Visit and your Interview User ID. Complete all following sections for this form:

b. Section A. Pregnancy Monitoring

- *If participant is female, collect information if she is of child bearing potential or reproductive and if she should be become pregnant during the study.*

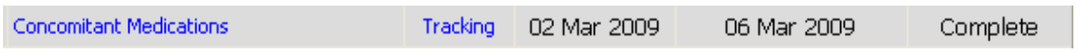


Step 4. After entering data, please reference section 9.1.4 Save and Close e-CRF form.

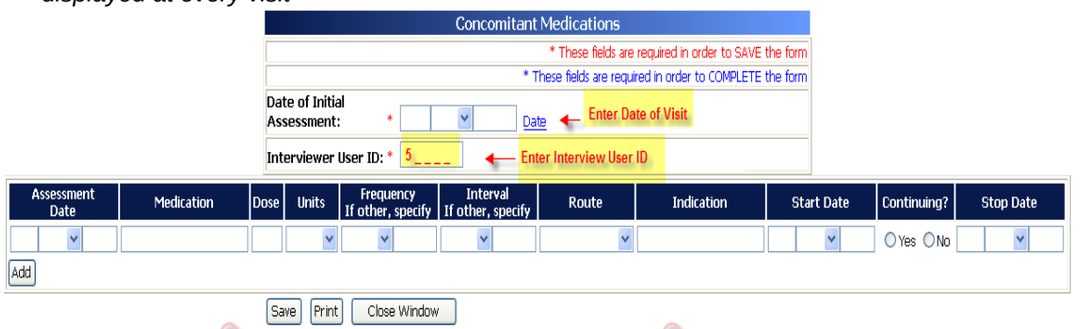
9.3.7 Concomitant Medications

Step 1. Procedure to enter data for Concomitant Medications: Be sure the Source Document is completed prior to completing forms

Step 2. Under Event Title - Select Concomitant Medications



Step 3. Once the form displays, enter Date of Visit and your Interview User ID Complete all following sections for this form: *Note: This is a running log. All data entered will be saved and displayed at all visits and will be displayed at every visit*



Step 4. After entering data, please reference section 9.1.4 Save and Close e-CRF form

9.3.7 Specimen Collection Forms: Autoantibodies, Chemistries, EBV/CMV, HIP/HepB/HepC, HLA, EBV Viral Load (EBV PCR), HbA1c, TNCC Serum PK/Cytokine, TNCC Serum Cytokines, TNCC Serum Immunogenicity, ITN Whole Blood – Plasma PBMC, ITN Whole Blood – RNA, TNCC Mechanistic Serum

Step 1. The following procedures will be the same for each specimen listed above. Be sure the Source Document is completed prior to completing the Specimen Collection Form

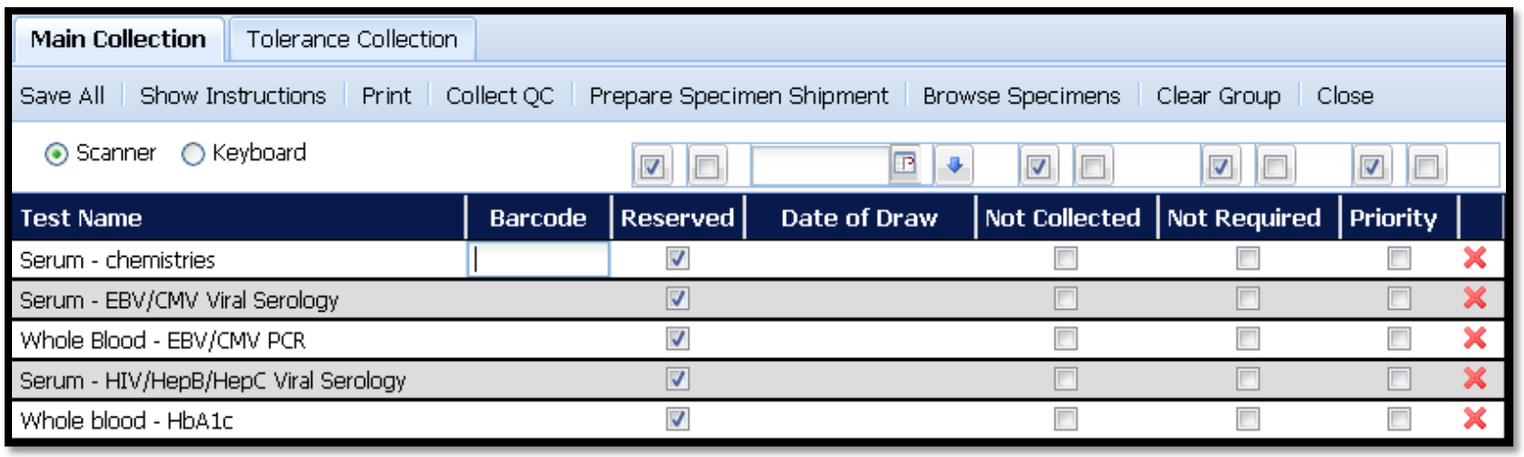
Step 2. Under Event Title: Select Specimen Collection Form. Collections that would be included in this procedure are by tab:

- **Main Collection: Autoantibodies**
- **Main Collection: Chemistries**
- **Main Collection: EBV/CMV Viral Serology**
- **Main Collection: EBV/CMV – Viral Load EBVPCR**
- **Main Collection: HIV/HEPB/HEPC**
- **Main Collection: HLA**
- **Tolerance Collection: MMTT**

- **Mechanistic Collection: Mechanistic Serum**
- **Mechanistic Collection: Whole Blood – Plasma/PBMC**

Step 3. Complete Specimen Information

i. Enter Barcode (scan or enter manually)
ii. Enter Date of Draw
iii. **Specify Priority for ALL Screening Samples**



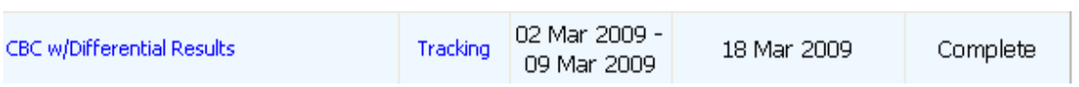
Step 4. After entering data, please reference section 9.1.4 Save and Close e-CRF form.

Step 5. Proceed to next tab in Specimen Collection Form

9.3.8 Specimen Collection Form: CBC with Differential

Step 1. Procedure to enter data for CBC with Differential: Be sure the Source Document is completed prior to completing forms

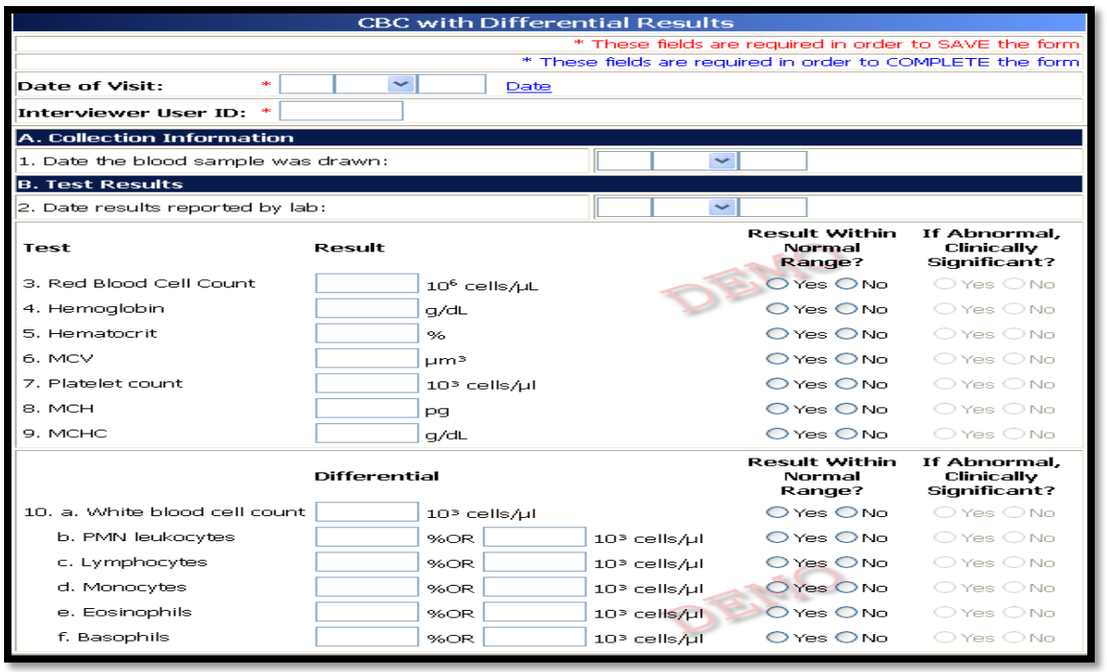
Step 2. Select Specimen Collection: CBC w/ Differential Results:



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

Note: Based on the results received from your site's lab the data can be entered in the following sections:

a. Section A: Collection Information
b. Section B: Test Results- data in these fields are based on the lab report provided by your local lab
   i. Indicate if result is within normal range based on your lab's normal ranges
   ii. If not within normal range, indicate if clinically significant or not



CBC with Differential Results

* These fields are required in order to SAVE the form

* These fields are required in order to COMPLETE the form

Date of Visit: * Date

Interviewer User ID: *

A. Collection Information

1. Date the blood sample was drawn:

B. Test Results

2. Date results reported by lab:

Test	Result		Result Within Normal Range?	If Abnormal, Clinically Significant?
3. Red Blood Cell Count		10^6 cells/µL	Yes No	Yes No
4. Hemoglobin		g/dL	Yes No	Yes No
5. Hematocrit		%	Yes No	Yes No
6. MCV		µm³	Yes No	Yes No
7. Platelet count		10^3 cells/µl	Yes No	Yes No
8. MCH		pg	Yes No	Yes No
9. MCHC		g/dL	Yes No	Yes No

Differential					Result Within Normal Range?	If Abnormal, Clinically Significant?
10. a. White blood cell count		10^3 cells/µl			Yes No	Yes No
b. PMN leukocytes		%OR		10^3 cells/µl	Yes No	Yes No
c. Lymphocytes		%OR		10^3 cells/µl	Yes No	Yes No
d. Monocytes		%OR		10^3 cells/µl	Yes No	Yes No
e. Eosinophils		%OR		10^3 cells/µl	Yes No	Yes No
f. Basophils		%OR		10^3 cells/µl	Yes No	Yes No

Step 4. After entering data, please reference section 9.1.4 Save and Close e-CRF form

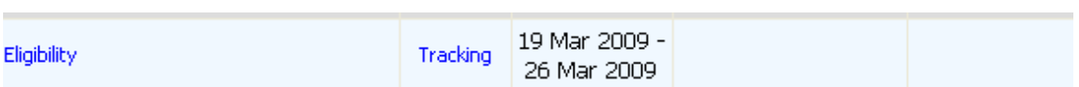
9.4 Baseline Visit

9.4.1 Eligibility

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

Step 1. Procedure to complete eCRF Eligibility: Be sure the Source Document is completed prior to completing this specimen collection form.

Step 2. Under the Event Title select: Eligibility



Eligibility	Tracking	19 Mar 2009 - 26 Mar 2009		

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

Step 4. Complete the following sections:

a. Section A. Inclusion Criteria
b. Section B. Exclusion Criteria
    i. If Female, answer questions 11-17

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

Step 6. Once in the Participant Details screen check to see if status of participant changed from Registered to Eligible.

Participant's Details

Participant ID:		Date of Registration:	
Local ID:		Letters:	
Status:	Eligible		
Site:			

9.4.2 Randomizing a Participant in the System

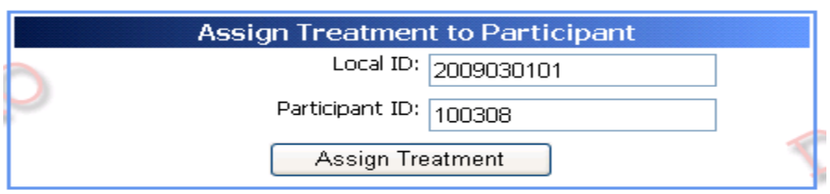
Step 1. Procedure to assign treatment and obtain randomization number: *the **Eligibility form must be complete** and the subject must be eligible prior to assigning treatment to/randomizing the subject.* From the left navigation menu select Assign Treatment

Note: At Baseline Visit, the Eligibility Form must be completed prior to assigning treatment.

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

Step 3. Select Assign Treatment

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



Treatment Assignment Successful. Randomization Id: 0006-001

Note: Each randomization number will only be assigned once

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

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

9.4.3 Interim Medical History

Step 1. Procedure to enter data for Interim Medical History: Be sure the Source Document is completed prior to completing this specimen collection form.

Step 2. Under the Event Title select: Interim Medical History

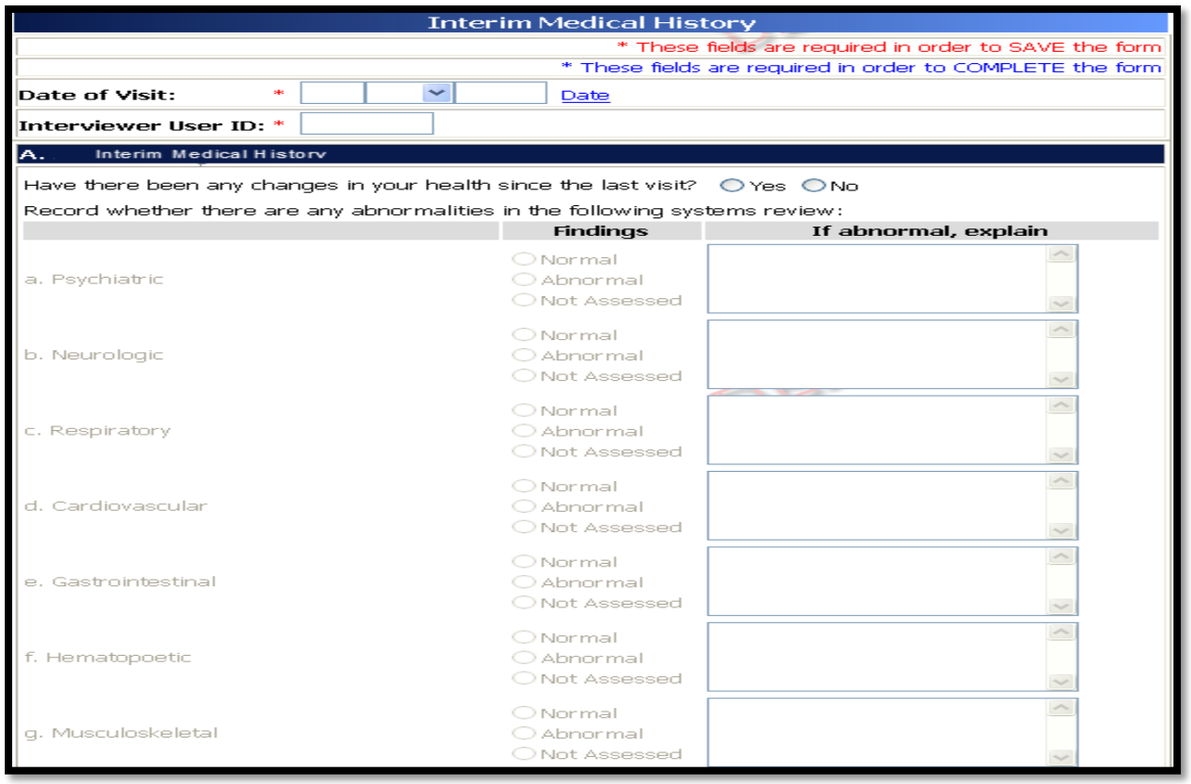
Interim Medical History	Tracking	19 Mar 2009		

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

Step 4. Complete the following sections:

i. Interim Medical History

ii. Vaccination Log



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

9.4.4 Physical Exam

Step 1. Procedure to enter data for Physical Exam: Be sure the Source Document is completed prior to completing forms

Step 2. Under Event Title - Select Physical Exam

Physical Exam	Tracking	02 Mar 2009 - 09 Mar 2009	24 Feb 2009	Complete

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

Step 4. Complete all following sections for this form:

i. Section A. Physical Exam

- *Collect participant's height, weight, and vitals (i.e. blood pressure) and any abnormalities found during the examination.*

9.4.5 Diabetes Management

Step 1. Procedure to enter data for Diabetes Management: Be sure the Source Document is completed prior to completing forms

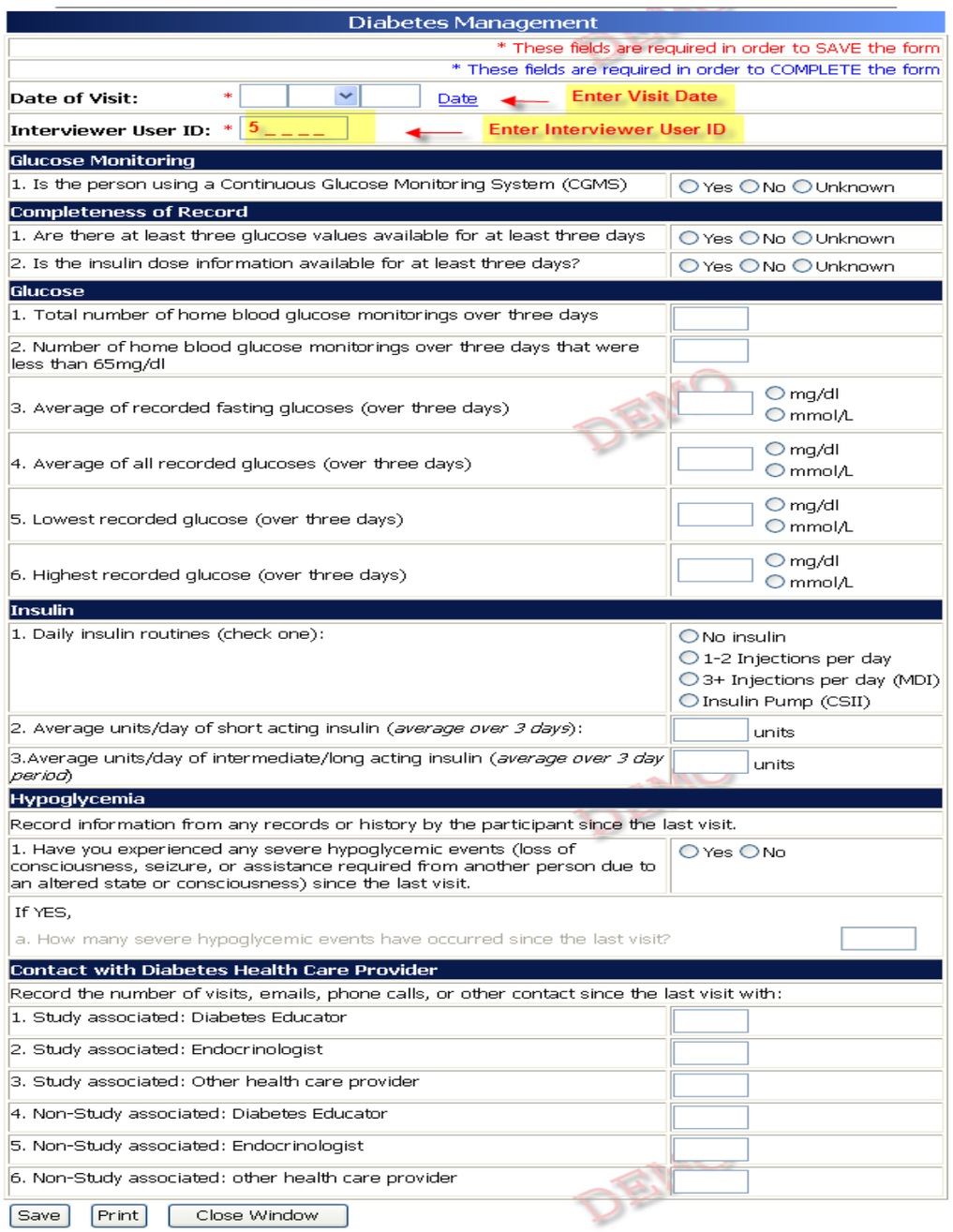
Step 2. Under Event Title - Select Diabetes Management

	Diabetes Management	Tracking	30 Aug 2010	30 Aug 2010 - 15 Sep 2010		

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

Step 4. Complete all following sections for this form and save:

i. Section A. Glucose Monitoring
ii. Section B. Completeness of Record
iii. Section C. Glucose
iv. Section D. Insulin
v. Section E. Hypoglycemia
vi. Contact with Diabetes Health Care Provider



Diabetes Management

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

Date of Visit: * Date ← Enter Visit Date

Interviewer User ID: * 5 _ _ _ _ ← Enter Interviewer User ID

Glucose Monitoring

1. Is the person using a Continuous Glucose Monitoring System (CGMS)	Yes No Unknown

Completeness of Record

1. Are there at least three glucose values available for at least three days	Yes No Unknown
2. Is the insulin dose information available for at least three days?	Yes No Unknown

Glucose

1. Total number of home blood glucose monitorings over three days	
2. Number of home blood glucose monitorings over three days that were less than 65mg/dl	
3. Average of recorded fasting glucoses (over three days)	mg/dl mmol/L
4. Average of all recorded glucoses (over three days)	mg/dl mmol/L
5. Lowest recorded glucose (over three days)	mg/dl mmol/L
6. Highest recorded glucose (over three days)	mg/dl mmol/L

Insulin

1. Daily insulin routines (check one):	No insulin 1-2 Injections per day 3+ Injections per day (MDI) Insulin Pump (CSII)
2. Average units/day of short acting insulin (*average over 3 days*):	units
3.Average units/day of intermediate/long acting insulin (*average over 3 day period*)	units

Hypoglycemia

Record information from any records or history by the participant since the last visit.

1. Have you experienced any severe hypoglycemic events (loss of consciousness, seizure, or assistance required from another person due to an altered state or consciousness) since the last visit.	Yes No

If YES,

a. How many severe hypoglycemic events have occurred since the last visit?

Contact with Diabetes Health Care Provider

Record the number of visits, emails, phone calls, or other contact since the last visit with:

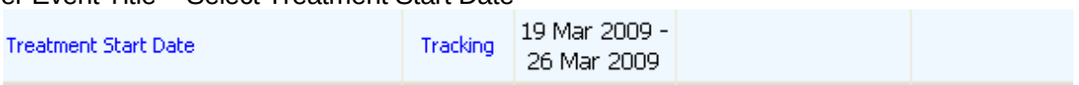
1. Study associated: Diabetes Educator	
2. Study associated: Endocrinologist	
3. Study associated: Other health care provider	
4. Non-Study associated: Diabetes Educator	
5. Non-Study associated: Endocrinologist	
6. Non-Study associated: other health care provider	

Save Print Close Window

9.4.6 Treatment Start Date (Only to be completed during Baseline Visit)

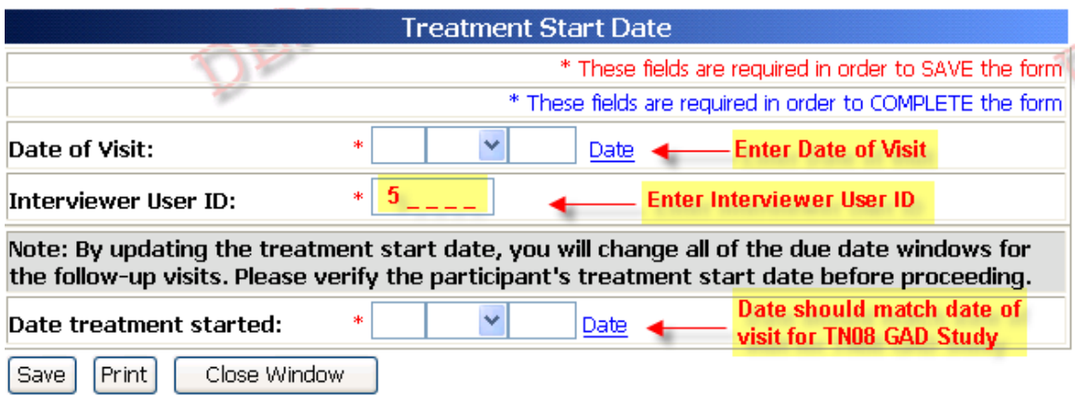
Step 1. Procedure to complete eCRF: Treatment Start Date: Be sure the Source Document is completed prior to completing forms

Step 2. Under Event Title - Select Treatment Start Date



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

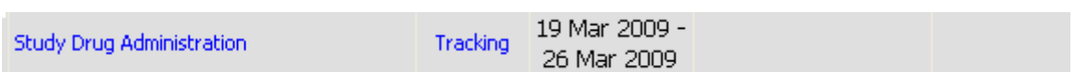
Step 4. Enter the date of treatment (should match the date of visit)



9.4.7 Study Drug Administration

Step 1. Procedure to enter data for Study Drug Administration: Be sure the Source Document is completed prior to completing forms

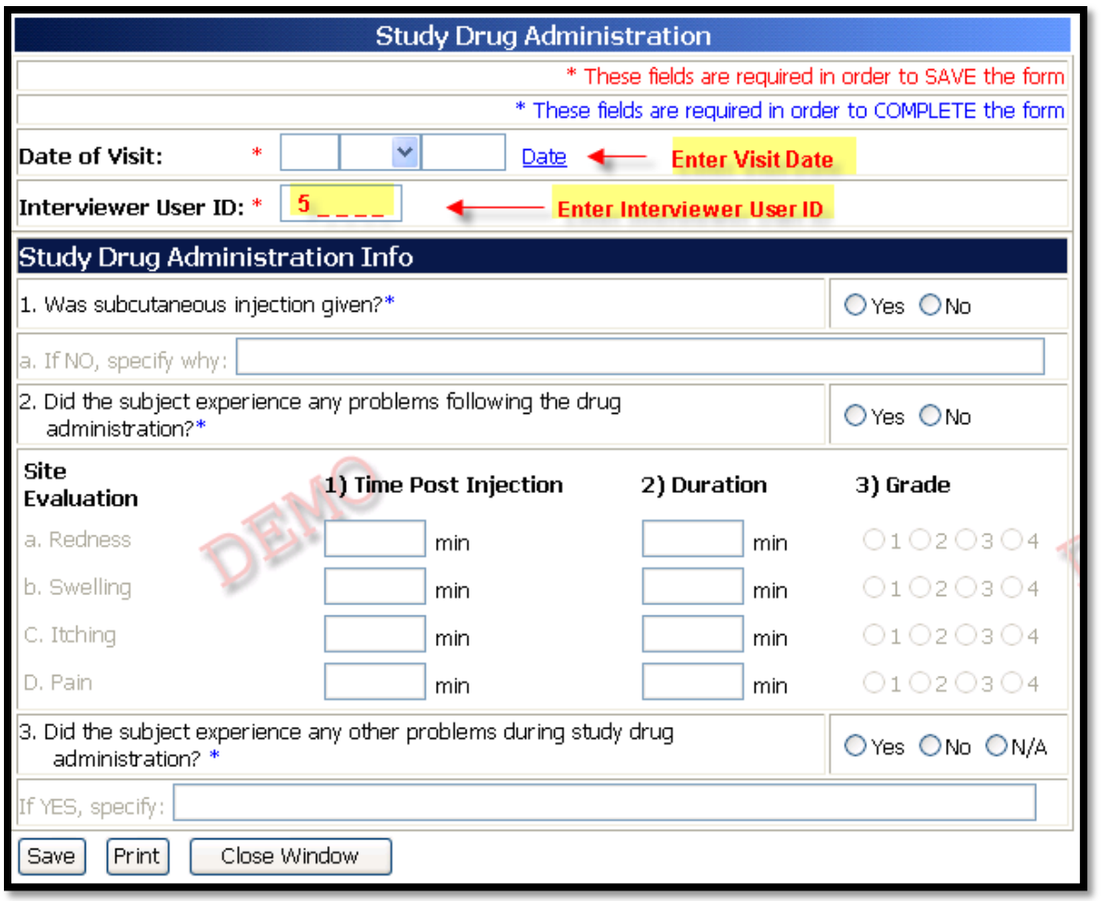
Step 2. Under Event Title - Select Study Drug Administration



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

Step 4. Complete all following sections for this form:

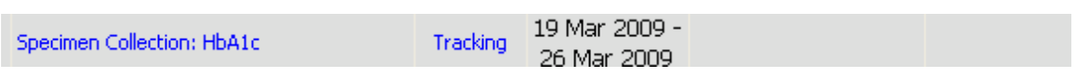
i. Section: Study Drug Administration Info: *Note: Question 1 and Question 2 must be answered in order to complete the form.*



9.4.9 Specimen Collection: HbA1c

Step 1. Procedure to enter data in the specimen collection form for HbA1c: Be sure the Source Document is completed prior to completing forms

Step 2. Under Event Title - Specimen Collection HbA1c



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

Step 4. Complete Specimen Information

a. Complete how specimen will be shipped to lab
b. Select Test Type: HbA1c
c. Barcode Label: Scan Vial

Package ID (if applicable) if shipping more than one vial of autoantibodies to lab indicate package ID (year/mm/dd/type of specimen)

Step 5. Complete Collection Information as was done for the screening visit

Once Baseline Visit is completed the rest of the visit windows will open for treatment and follow up visits:

9.5 Visits 2-19: Other Study Visits

All other study visits (visits 2-19) use the same or similar forms as described above.

9.6 Additional Study Forms/Events (PRN)

9.6.1 List and Definitions of PRN Forms

Definition: PRN – "When necessary"

The forms available under the **Additional Study Forms/Events** are an on needed basis. Forms available are as follows:

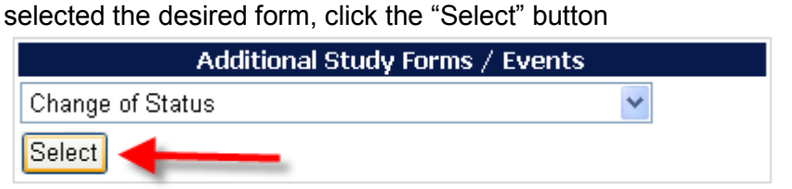
1. Change of Status form: Status of the participant changes (subject withdrawals from study or is lost to follow up, ect).
2. Diabetes Management: blood glucose monitoring and insulin regimen data since last visit
3. Interim Medical History: updated medical information since last visit
4. Mortality Event: a subject dies
5. Optional Visit 6a: Complete for subjects who agree to have optional visit 6a 2 hr MMTT
6. Physical Exam: updated information since last physical examination
7. Permanent Participant Site Transfer: a subject moves from one study site to another
8. Pregnancy Confirmation: a participant is determined to be pregnant
9. Pregnancy Monitoring: completed for female subjects with reproductive potential
10. Pregnancy Outcome: the outcome of the pregnancy at pregnancy end point (meaning, the subject gives birth, miscarries, etc)
11. Pre-Randomization Exit Form: if a subject doesn't complete the screening because they are found to be ineligible or withdraw consent sites would complete this form
12. Protocol Deviation: a protocol deviation occurs (subject is dosed from wrong kit, assessments or assays are not done, etc)
13. Report New Adverse Event: a subject experiences a reportable adverse event
14. Two Week Post Positive EBVPCR Confirmatory Testing: this should be completed for subjects who seroconvert on study and will need to follow the viral monitoring algorithm of having an EBVPCR test done at 2 weeks, then 4, 8, and monthly thereafter All Study Specimen Collection Forms: A specific specimen was not collected due to a missed visit or if participant is unable to provide specimen during scheduled visit

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

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

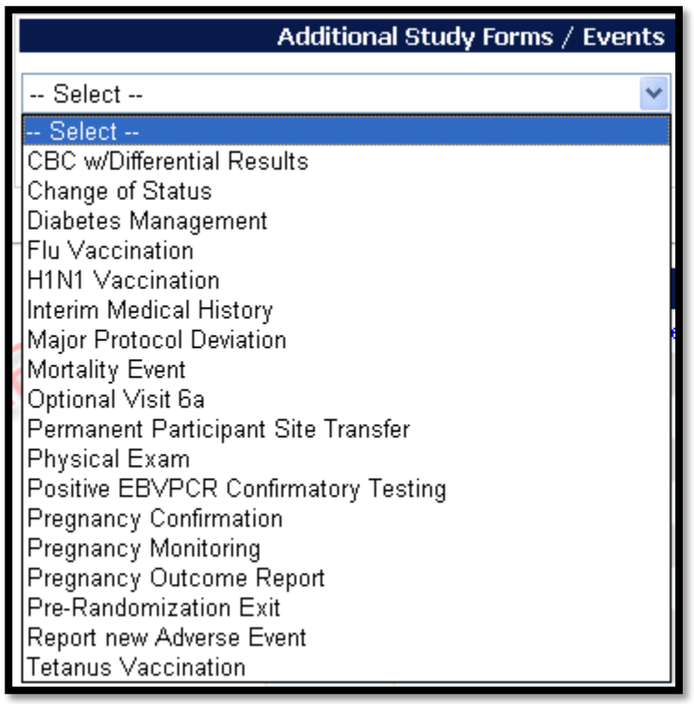
Step 3. Once you have selected the desired form, click the "Select" button



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

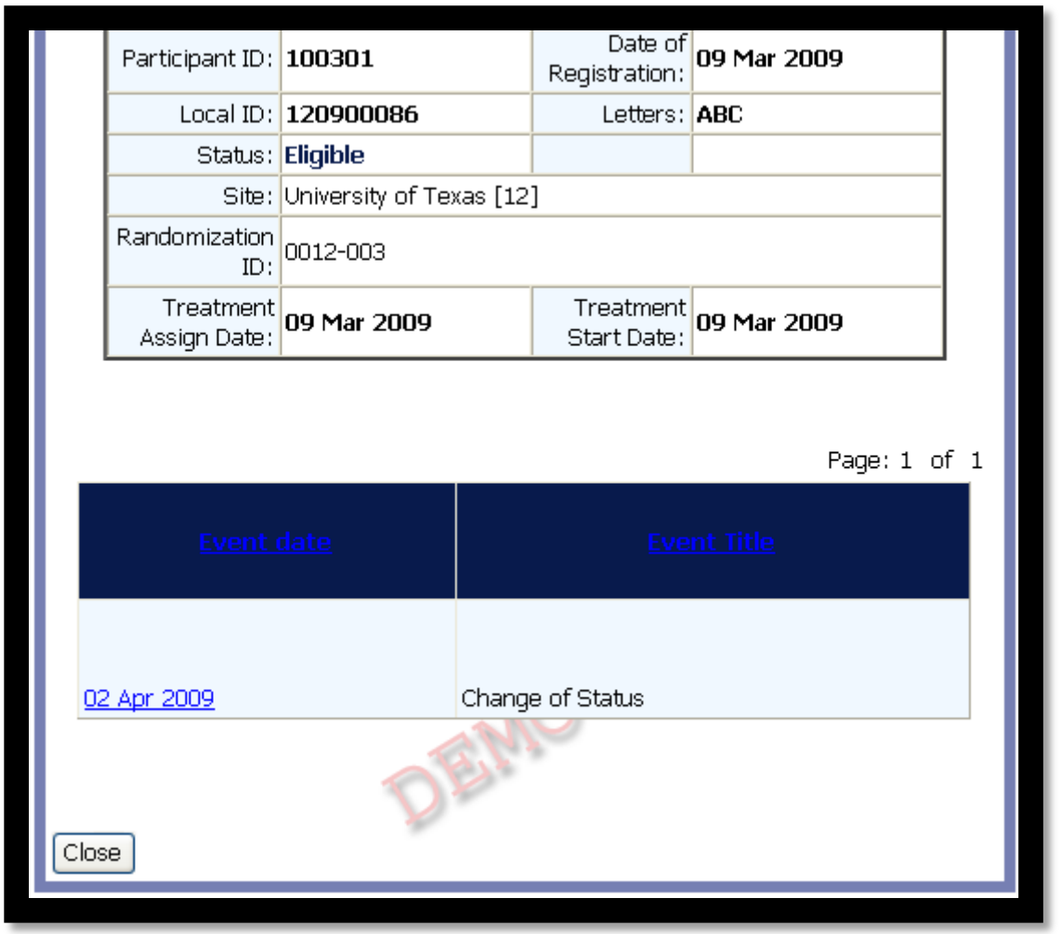
9.6.3 Open a Previously Completed Additional Study Form/Event (PRN Form)

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



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

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



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

10. ADVERSE EVENT REPORTING PROCEDURES

All adverse events (defined below) will be reported to the TrialNet Data Safety and Monitoring Board (DSMB) by using the Adverse Events Data Management System (AEDAMS) described below this section is in 4 parts:

1. The first describes network definitions for adverse event types and descriptions of required data elements.
2. The second describes the reporting requirements of the network
3. The third section of this chapter describes how to use the TNCC's Adverse Events Data Management System (AEDAMS) to report to the network.
4. The final section briefly describes the handling of reported adverse events by the automated Adverse Events Reporting Management System and the DSMB.

10.1 Definitions and Data Descriptions

TrialNet defines an adverse event as: "…any occurrence or worsening of an undesirable or unintended sign, symptom or disease whether or not associated with the treatment and study procedures."

The operational definition for serious adverse events that TrialNet uses is a bit broader than the definition often used for purposes of regulatory reporting. 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 that TrialNet is using to report adverse events will be the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, with the exception of hypoglycemia and hyperglycemia, developed and maintained by CTEP at National Cancer Institute. This classification provides a grade (1-5) to describe event severity; the severity grade determines whether an event is considered "serious" for purposes of TrialNet DSMB review.

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.

Throughout the study, the investigator must record all adverse events on source documentation, and those that are Grade 2 or greater must be recorded 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. **If there is any question as to whether an event is reportable or any general questions you may have about adverse events please contact the TNCC protocol CRA.**

Adverse events may be discovered through:

- observation of the participant;
- questioning the participant;
- unsolicited complaint by the participant.

In questioning the participant the questioning should be conducted in an objective manner.

For this trial, an adverse event associated with the treatment or study procedures that suggests a significant hazard, contraindication, side effect or precaution (as described below) is to be reported as a serious adverse event (SAE). A serious adverse event (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 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 or informed consent document for a particular protocol required intervention.

Data Descriptions

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

been approved by all TrialNet investigators, the TrialNet Executive Committee, and the TrialNet Data and Technology Coordinating Center (TNCC).

Common Terminology Criteria for Adverse Events (CTCAE)

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

The CTCAE is organized broadly by categories (28), shown below:

Allergy/Immunology	Gastrointestinal	Pain
Auditory/Ear	Growth & Development	Pulmonary/Upper Resp.
Blood/Bone Marrow	Hemorrhage/Bleeding	Renal/Genitourinary
Cardiac Arrhythmia	Hepatobiliary/Pancreas	Secondary Malignancy
Cardiac General	Infection	Sexual/Reprod. Function
Coagulation	Lymphatics	Surgery/Intra-Oper. Injury
Constitutional Sympt.	Metabolic/Laboratory	Syndromes
Death	Musculoskeletal/Soft Tissue	Vascula
Dermatology/Skin	Neurology	
Endocrine	Ocular/Visual	

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

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

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

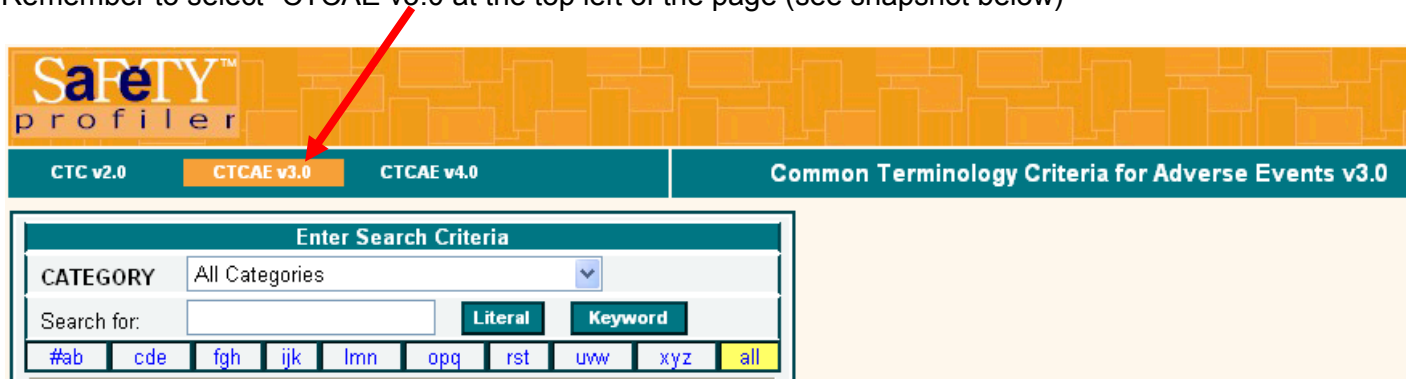
Using the CTCAE

TrilaNet provides several resources for the proper use of CTCAE codes for adverse event reporting. Because the NCI has developed and maintained the CTCAE classification, the recommended educational materials are from the NCI. Each person entering data in the protocol should be given a copy of a small spiral-bound booklet titled "Common Terminology Criteria for Adverse Events (CTCAE), version 3.0." [NIH Publication No. 03-5410.] This booklet contains the entire CTCAE, with descriptions of each event and grade.

Additionally, the CTCAE can be accessed online from the NCI at:
http://ctep.cancer.gov/forms/CTCAEv3.pdf

Another useful tool to assist in the categorization of an AE is the **Safety Profiler**.
http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx

Remember to select "CTCAE v3.0 at the top left of the page (see snapshot below)



Please note that the semicolons (;) in the descriptions equate to the word "or". For instance if you were trying to categorize an allergic reaction and determined that it was a grade 2. Interpret the description as Rash OR Flushing OR Urticaria… The participant does not need to meet all terms listed within a description; just one.

Adverse Event Details

CATEGORY: ALLERGY/IMMUNOLOGY
Adverse Event: Allergic reaction/hypersensitivity (including drug fever)
Short Name: Allergic reaction
MedDRA Code: 10020751

Grade	Description
1	Transient flushing or rash; drug fever < 38 degrees C (< 100.4 degrees F)
2	Rash; flushing; urticaria; dyspnea; drug fever >=38 degrees C (>=100.4 degrees F)
3	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension
4	Anaphylaxis
5	Death

Also Consider:

Adverse Event	Description	Category
Cytokine release syndrome	Cytokine release syndrome/acute infusion reaction	SYNDROMES

Remark:

Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity (including drug fever).

* MedDRA Version 10.0

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

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

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

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

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

The NCI also posts an Index to the CTCAE at: http://ctep.cancer.gov/forms/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

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

10.2.1 Procedures For Inquires Regarding Adverse Events

If the Principal Investigator and/or Study Coordinator has an inquiry regarding an adverse event, such as "subject had an event that may be possibly related to study drug how should this be reported?", these types of inquiries must be communicated directly to the TNCC CRA first.

10.3 Directions for Reporting AE's / System Description

Step 1. Log in with your User Name and Password.

10.3.1 Navigating to the Adverse Event Form

Step 2. Once you have successfully logged into the members website, the first page you will view is the Members Home Page.

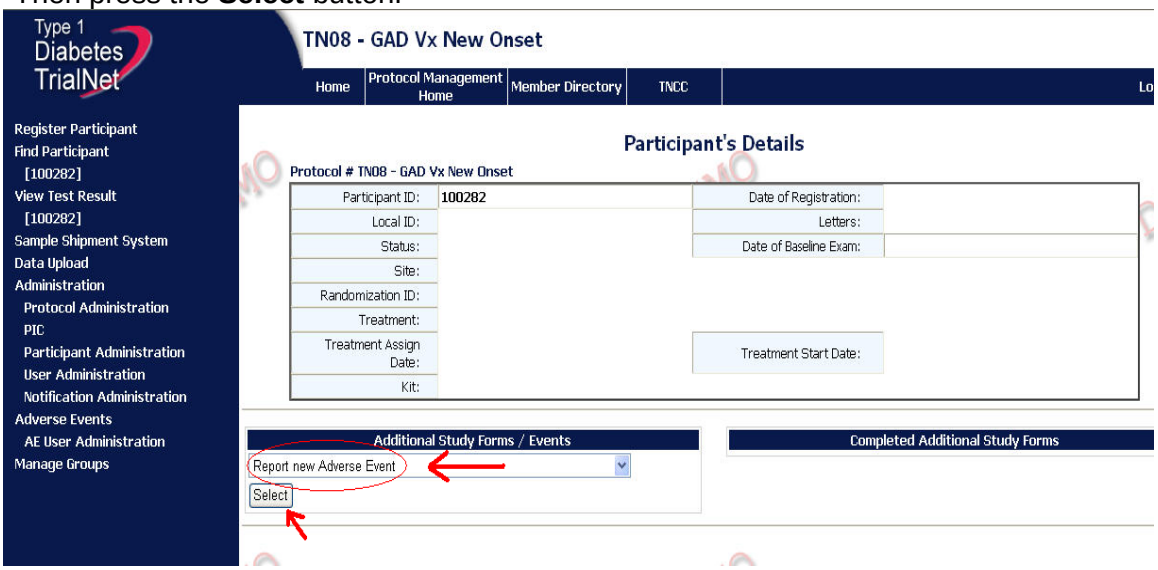
Step 3. From the left navigation menu on the main page, Select TN14 ANTI IL-1BETA Vx New Onset.

Step 4. A new window opens to the TN14 ANTI IL-1BETA Vx New Onset study.

Step 5. After you find the pertinent participant from the Find a Participant page, click on the Local ID link (in blue) for the participant.

Step 6. The Participant's Details page is now displayed.

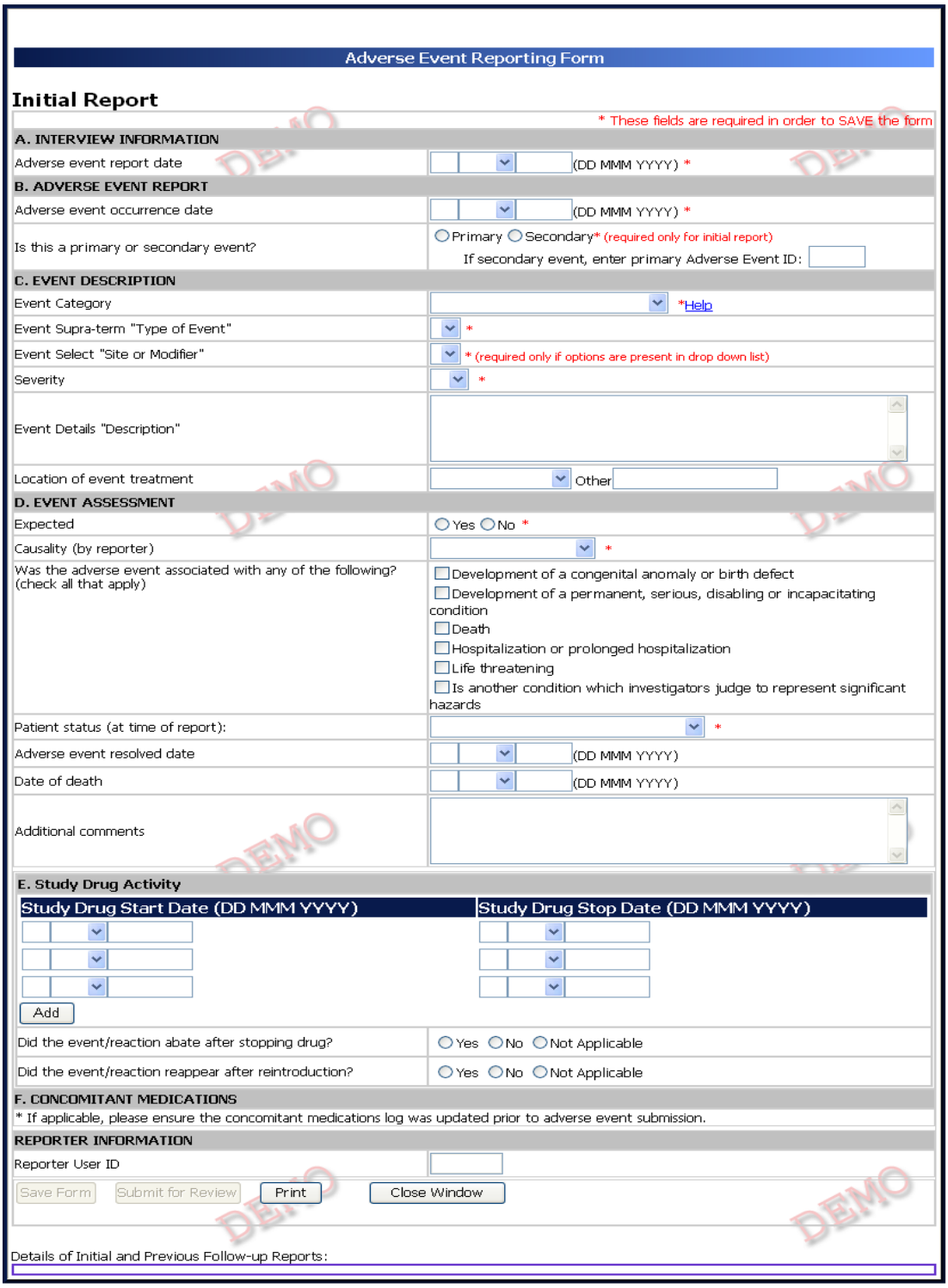
Step 7. Select "Report new Adverse Event" from the **Additional Study Forms/Events** dropdown list. Then press the **Select** button.



10.3.2 Reporting an Adverse Event

Step 8. 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, click on the save button. If the save is successful, you will see a success message. You may then close this window. If

you do not see a success message, your report was not transmitted. Please resave, or contact your TNCC CRA immediately for assistance.



Adverse Event Reporting Form

Initial Report

* These fields are required in order to SAVE the form

A. INTERVIEW INFORMATION

Adverse event report date (DD MMM YYYY) *

B. ADVERSE EVENT REPORT

Adverse event occurrence date (DD MMM YYYY) *

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

C. EVENT DESCRIPTION

Event Category *Help

Event Supra-term "Type of Event" *

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

Severity *

Event Details "Description"

Location of event treatment Other

D. EVENT ASSESSMENT

Expected Yes No *

Causality (by reporter) *

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

Patient status (at time of report): *

Adverse event resolved date (DD MMM YYYY)

Date of death (DD MMM YYYY)

Additional comments

E. Study Drug Activity

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

Add

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

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

F. CONCOMITANT MEDICATIONS

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

REPORTER INFORMATION

Reporter User ID

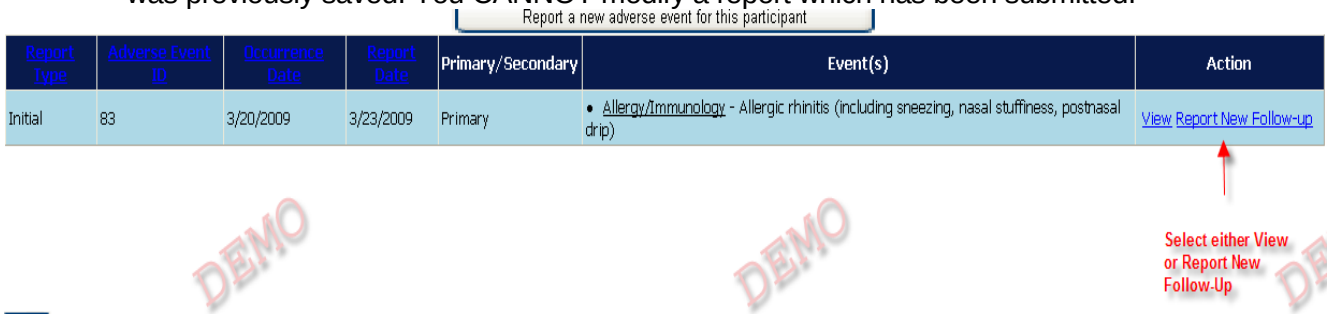
Save Form Submit for Review Print Close Window

Details of Initial and Previous Follow-up Reports:

10.3.3 Viewing and Editing Previously Reported Adverse Events

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

Step 2. The Adverse Event Form List will appear. This page lists previously reported adverse events for this participant. Click on the blue Adverse Event ID # to view each report. You can modify a report if it was previously saved. You CANNOT modify a report which has been submitted.



10.4 Overview of Handling of Reported Adverse Events

The adverse events form will be available to investigators and delegated personnel at all study sites. As with all other aspects of the TNCC provided protocol management tools, the Adverse Events Data Management System is a secure web site with password access.

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

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), FDA, and local IRBs for any institution where an adverse event occurs.

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

10.5 Reporting to the FDA

In addition to the reporting requirements for the TrialNet network (as described above) the FDA requires reporting of any adverse event which is both serious and unexpected (21CFR312.32 (c)(i)(A)-(B)). For TN14 specifically the FDA has asked that sites report any serious infections and are regarded as SAE(s) to the FDA even if the event is an SAE and does not answer yes to all the following questions:

- Is the adverse event unexpected?
- Is the adverse event related or possibly related to participation in the research?
- Does the adverse event suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized?

The process for reporting to the FDA is as follows:

1. Sites completes 3500A MedWatch report (mandatory reporting form).
    a. Link to form: http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM082728.pdf
    b. *Link to online form: https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm
    c. Instructions for completing form: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/ucm149238.htm
2. Site emails completed 3500A MedWatch report to TNCC CRA and TrialNet Medical Monitor (Brett J. Loechelt, MD; bloechel@cnmc.org)
3. Within 7 days of being notified of the event, the site sends the 3500A MedWatch report to FDA https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm

Please submit completed 3500A MedWatch Reports via fax to: 1-800-FDA-0178

Or mail to:
MedWatch
5600 Fishers Lane
Rockville, MD 20852-9787

You may contact the FDA by phone at **301-796-3400** to confirm receipt of report.

***If MedWatch Online Electronic Submission of 3500A Form:** If you have provided the correct e-mail address in section E [reporter information] of the MedWatch 3500A form, you will receive an e-mail confirming receipt of your submission.

If you do not receive this e-mail confirmation within several hours, your report may not have been received. Please call the phone number provided above to confirm receipt of report.

11. Protocol Manager: Folders and Tools

Under the “Document Navigation” section of the Protocol Manager area are a series of folders meant to assist/aid sites in the conduct of the study.

11.1. TN14 – (A) Documents for IRB Submission Folder

This folder contains all the latest documents that may require submission to your local IRB(s). Containing the following subfolders:

- 01. Protocol Folder
- 02. Consent & Assent Templates Folder
- 03. Investigator Brochure Folder
- 04. Quizzes & Surveys Folder
- 05. Recruitment Materials Folder
- 06. Blood Volume Tables

11.2. TN14 – (B) Documents for Training & Guidance Folder

This folder contains the latest documents for training and guidance. Containing the following subfolders:

- 01. Manual of Operations Folder
- 02. Pharmacy Manual Folder
- 03. Laboratory Manual Folder
- 04. Reimbursement Schedule Folder

11.3. TN14 – (C) Forms

This folder contains the latest versions of the TN14 forms. Containing the following subfolders:

- 01. Site Initiation Folder
- 02. Assessment Tools Folder
- 03. Visit Checklists Folder
- 04. Pharmacy Forms Folder
- 05. Laboratory Forms Folder
- 06. FDA Forms Folder
- 07. Supplies Folder

11.4. TN14 – (D) Adverse Events Folder

This folder contains all external adverse events (IND Safety Reports) that have occurred since study activation and a listing of all Serious Internal Adverse Events. Containing the following subfolders:

- External Adverse Events (IND Safety Reports) Folder

- Internal Adverse Events Folder

11.5. TN14 – (E) Reports Folder

This folder contains all general reports and site specific reports:

Current Documents Available in TN14 – Reports Folder:

- Archive – old TNCC Reports
- Barbara Davis Center for Childhood Diabetes [7]
- Benaroya Research Institute [10]
- Columbia University [15]
- General Reports
- Indiana University – Riley Hospital for Children [16]
- Stanford University [5]
- The Hospital for Sick Children [13]
- University of California – San Francisco [11]
- University of Florida [1]
- University of Miami [6]
- University of Minnesota [9]
- University of Pittsburgh [14]
- University of Texas Southwestern [12]
- Vanderbilt Eskind Diabetes Clinic [3126]
- Yale University [2]

11.6. General Reports (All Sites)

For all TN14 TNCC Reports available to sites proceed to the Reports folder

→TN14 – Anti IL-1Beta (Canakinumab) Protocol Management Home → TN14 – (E) Reports → General Reports

Current Documents Available in General Reports Folder (these reports include data from all sites):

- TN14 Accrual Report by Clinical Center
- TN14 Actual vs. Expected Accrual – Graph
- TN14 IRB Summary – Ethnicity, Race, and Gender Report
- TN14 Adverse Event Summary Report

11.7. Reports in Each Site Folder

For individual site reports proceed to the "Site Name [**#**]" folder – Site staff will only have access to their site respective folder

→TN14 – Anti IL-1Beta (Canakinumab) Protocol Management Home → TN14 – (E) Reports → Your Site Name [Your Site #]

Current Documents Available in your site's folder:

- Site Accrual Report
- Site IRB Summary – Ethnicity, Race, and Gender Report
- Site Adverse Event Summary Report
- Site Scheduling Calendar
- Site Participant Schedule of Visits Report

11.8. TN14 – (F) Study Group Calls & Meetings

For study group meeting/call agendas, minutes, call recordings proceed to the TN09 – Study Group Meetings folder

→TN09 TN14 – Anti IL-1Beta (Canakinumab) Protocol Management Home → TN14 – (F) Study Group Meetings & Meetings

Current Documents Available in the TN14 – Study Group Meetings folder:

- 2010
  - 2010 Agenda Items
  - 2010 Agendas
  - Minutes
    - Conference Call Recordings

11.9. TN14 – (G) Announcements

This folder contains study announcements.

An additional folder has been added titled **TN14 – (H) FAQ(s)** that will provide frequently asked question guidance to sites.

12. Supplies

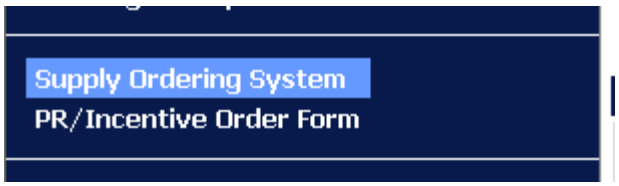
12.1 Ordering Supplies- Test/Assay Collection and Shipment

All supplies for Test/Assays (collection and shipment) are either ordered from ITN or through the Fisher online supply ordering system.

All Other Assays/Tests - Fisher

The TNCC reviews all orders placed within 48 hours. USF TNCC orders the etched vials directly from a third party vendor and approves all supply orders in the Fisher system

Step 1. From the main members' web page, on the left side navigation menu, select "Supply Ordering System"



Step 2. A new window will open. You will be prompted to enter your TrialNet Supply Order System Login.
Note: If you do not have a login, please contact the TNCC to obtain a login.

Step 3. Select the Study for which you want to order supplies

Step 4. Select the supplies- by test/assay- you wish to order

Step 5. Indicate- at the end of the order- the date by when the supplies are needed.

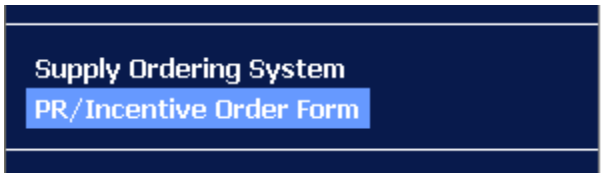
Step 6. Submit your order.

12.2 Ordering Study Agent

Please refer to the Pharmacy Manual of Operations

12.3 Ordering Incentives

Step 1. From the main members' web page, on the left side navigation menu, select "PR/Incentive Order Form"



Step 2. A PDF order form will open in a new window. Complete all fields and send form to contact information - TNCC

13. Cytochrome P450 Drug Interactions

All subjects using warfarin will be excluded from the study so we are providing sites with a list of CYP450 substrates and ask that all medications used by subjects be checked against this list to determine whether use is appropriate. If there is such use, the PI should decide if any of these meds require frequent and close monitoring and discuss with subject and subject's treating physician (by assessment of either biomarkers [coagulation factors] or drug levels if a biomarker is not available) of individuals concomitantly treated with agents that are substrates for CYP450. We do note, however, that this is a theoretical concern as to date there is no evidence (not only for canakinumab, but also for other monoclonal antibodies) to suggest that the in vitro findings would translate into any clinically significant effect. See below for list of cytochrome P450 Substrates.

SUBSTRATES

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
amitriptyline caffeine clomipramine clozapine cyclobenzaprine estradiol fluvoxamine haloperidol imipramine N-DeMe mexilletine naproxen olanzapine ondansetron phenacetin_ acetaminophen→NAPQI propranolol riluzole ropivacaine tacrine theophylline tizanidine verapamil (R)warfarin zileuton zolmitriptan	bupropion cyclophosphamide efavirenz ifosfamide methadone	paclitaxel torsemide amodiaquine cerivastatin repaglinide	**NSAIDs:** diclofenac ibuprofen lornoxicam meloxicam S-naproxen_Nor piroxicam suprofen **Oral Hypoglycemic Agents:** tolbutamide glipizide **Angiotensin II Blockers:** losartan irbesartan **Sulfonylureas:** glyburide glibenclamide glipizide glimepiride tolbutamide amitriptyline celecoxib	**Proton Pump Inhibitors:** lansoprazole omeprazole pantoprazole rabeprazole **Anti-epileptics:** diazepam→Nor phenytoin(O) S-mephenytoin Phenobarbitone amitriptyline carisoprodol citalopram chloramphenicol clomipramine cyclophosphamide hexobarbital imipramine N-DeME indomethacin R-mephobarbital moclobemide nelfinavir nilutamide primidone progesterone proguanil	**Beta Blockers:** carvedilol S-metoprolol propafenone timolol **Antidepressants:** amitriptyline clomipramine desipramine imipramine paroxetine **Antipsychotics:** haloperidol perphenazine risperidone→9OH thioridazine zuclopenthixol alprenolol amphetamine aripiprazole atomoxetine bufuralol chlorpheniramine chlorpromazine codeine (→O-desMe) debrisoquine	**Anesthetics**: enflurane halothane isoflurane methoxyflurane sevoflurane acetaminophen→ NAPQI aniline2 benzene chlorzoxazone ethanol N,N-dimethyl formamide theophylline→ 8-OH	**Macrolide antibiotics:** clarithromycin erythromycin (not 3A5) NOT azithromycin Telithromycin **Anti-arrhythmics:** quinidine→3OH (not 3A5) **Benzodiazepines:** alprazolam diazepam→3OH midazolam triazolam **Immune Modulators:** cyclosporine tacrolimus (FK506) **HIV Antivirals:** indinavir nelfinavir ritonavir saquinavir **Prokinetic:** Cisapride

			fluoxetine fluvastatin glyburide nateglinide phenytoin-4-OH2 rosiglitazone tamoxifen torsemide S-warfarin	propranolol teniposide R-warfarin→8-OH	dexfenfluramine dextromethorphan duloxetine encainide flecainide fluoxetine fluvoxamine lidocaine metoclopramide methoxyamphetamine mexilletine minaprine nebivolol nortriptyline ondansetron oxycodone perhexiline phenacetin phenformin promethazine propranolol sparteine tamoxifen tramadol venlafaxine		**Antihistamines:** astemizole chlorpheniramine terfenadine **Calcium Channel Blockers:** amlodipine diltiazem felodipine lercanidipine nifedipine2 nisoldipine nitrendipine verapamil **HMG CoA Reductase Inhibitors:** atorvastatin cerivastatin lovastatin NOT pravastatin Simvastatin **Steroid 6beta-OH:** estradiol hydrocortisone progesterone testosterone **Miscellaneous:** alfentanyl aprepitant aripiprazole buspirone cafergot caffeine_TMU cilostazol cocaine codeine-Ndemethylation dapsone dexamethasone dextromethorphan docetaxel domperidone eplerenone

							fentanyl finasteride gleevec haloperidol irinotecan LAAM lidocaine methadone nateglinide ondansetron pimozide propranolol quetiapine quinine risperidone NOT rosuvastatin salmeterol sildenafil sirolimus tamoxifen taxol terfenadine trazodone vincristine zaleplon ziprasidone zolpidem

14. Appendix A: TrialNet Site Audits

14.1. Audit Information Sheet

Hints for Preparing for the Audit:

Please review your study specific regulatory binder to make sure you have copies of the following:

- NIH approved protocol with all addenda
- All essential documents
    - Site Delegation Log
    - CVs of all study staff
    - Human Subjects Education Certificates of all study staff
    - If an interventional study, most current Investigational brochure
    - Completed & signed 1572* (see section 14.3 on Draft FDA instructions on completing a 1572 form)

- Please have the following available for review:
    - Copies of the Electronic Case Report Forms (either access to internet **OR** hard copies)
    - Original medical record (source documents) for each participant case being audited
    - Informed consent forms for all participant cases being audited (please make sure that the consenting process has been documented – see section 14.4 for guidance)
    - Completed volunteer assessment (please be sure to review the questions and answers with the participant and/or legal guardian(s)/parent(s) to ensure they understand the study and their participation in the study, document the review process thoroughly – see section 14.5 for guidance)
    - Documentation of IRB approval for the protocol being audited
        - original protocol approval
        - all amendment approvals
        - annual re-approval
        - all approved informed consent forms

It is recommended that proof of eligibility and all eligibility requirement documentation, laboratory results and study visit notes be consistently organized in the source documentation.

Source documentation of the following should be available (PI should sign and date eligibility source documentation):

- **Type 1 diabetes within 100 days of randomization (randomization within 37 days of MMTT),**
- **Age 6-45,**
- **At least one diabetes associated autoantibody (If only MIAA positive must have an additional autoantibody present if taking insulin therapy >7 days),**
- **C-peptide levels ≥ 0.2 pmol/ml MMTT,**
- **Chemistries results prior to 100 day window expiration**
- **HIV negative,**
- **HepBC negative,**
- **EBVIGM negative,**
- **EBVVL negative,**

- **PPD negative,**
- **Weigh at least 20 kg /44lbs at study entry**

Please note that all data must be entered into the electronic case report form within 30 days of the subject's visit.

At time of audit:

- *If forms have not been complete within 30-59 days, this is considered to be a minor delinquency.*
- *If forms have not been complete within 60+ days, this is considered to be a major delinquency.*

After the Audit:

If the audit findings reveal an Acceptable, that Needs Follow Up or Unacceptable Determination the Principal Investigator must respond to the TNCC Lead Auditor 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.

Filing Audit Related documents:

Do not ever file the audit reports in your study regulatory files. The audit reports must be filed independently of the study. You will need to retain the audit report for the as long as the study records are retained.

Do not file audit related correspondence (letter and/or e-mails) in your study regulatory files.

14.2. Audit Guidelines – Version March 27, 2009

INTRODUCTION

The TrialNet Data and Technology Coordinating Center (TNCC) audit site visit guidelines are in accordance with the NIH NCI-CTMB Guidelines for monitoring of clinical trials for cooperative groups, last revised October 2006, located at http://ctep.info.nih.gov/monitoring/2006_ctmb_guidelines.pdf

COMPONENTS OF AN AUDIT SITE VISIT

- Subject case records
- Pharmacy operations and IND accountability, if applicable
- Regulatory compliance – IRB documentation and informed consent content

SELECTION OF INSTITUTIONS/INVESTIGATORS

Observational Studies:

All TrialNet (TN) sites will be audited. Sites will be eligible for an audit site visit within 18 months of their first subject accrual to any TrialNet study. At the time of the audit site visit, all TrialNet studies that have accrued subjects will be reviewed. Thereafter, observational studies will be audited within 3 years of the last successful audit date.

If audit findings require follow-up to assess resolution of problems identified at a previous audit, a re-audit will be conducted (usually at 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 3 years of the successful audit date.

Prevention and Intervention Studies:

All TrialNet interventional studies will be audited. Studies will be eligible for an audit site visit within 18 months of the first subject accrual and semi-annually thereafter. Studies that accrue rapidly or have a large number of subjects on-study or in follow-up may be audited more frequently.

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.

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.

AUDIT TEAMS

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.

Local IRB representatives may observe the audit.

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.

ARRANGING THE AUDIT

An audit date mutually convenient to the audit team and the site will be selected. A list of announced cases will be sent to the site no less than 14 days in advance of the audit to allow time for record preparation.

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.

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 per study.

The site is responsible for ensuring that all relevant materials are available for review at the time of the audit.

SELECTION OF CASES

The TNCC will select all cases for all audits.

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 less than 5 subjects have been accrued at the site, then all cases will be audited. If an audit of unannounced cases is warranted, at least one or more additional cases will be selected at the time of the audit visit. 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%.

For the TrialNet Natural History study only, selection of cases will be based on enrollment by phase instead of total enrollment. For phase 1, 1% of enrolled subjects will be audited. For phase 2, 10% of enrolled subjects will be audited. For phase 3, 10% of enrolled subjects will be audited.

Routine audit site visits will review 10% of the total cases accrued since the initial audit site visit. If no new cases have been accrued since the initial audit site visit, then only data collected since the initial audit site visit will be reviewed in the existing case records. Selected cases are typically those accrued since last audit; however, any case is subject to audit.

PREPARATION BY THE INSTITUTION BEING AUDITED

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 site person should be available to answer questions from the audit team for the duration of the audit site visit.

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.

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:

- Orientation by the site staff to the organization of the source documents and case report forms (research study charts)
- 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.
- Original source documents for each subject being audited
- All subject consent forms
- Documentation of IRB approval for all protocols being audited

Including: original protocol approval, all amendment approvals, and annual re-approval

- Most current copy of each protocol with all addenda
- † A visit to the pharmacy should be scheduled 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.
- 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.
- Source documentation should be organized so that auditors can easily identify them.

REQUIRED DOCUMENTS

The TrialNet site is expected to have study regulatory files with the following information:

Essential documents including:	• Principal Investigator and sub-investigators' Curriculum vitae • † Principal Investigator 1572 • Proof of Human Subject Protection education training for PI and all research staff handling subject data • Site Delegation Log • Letters of initial and continuing IRB approval • IRB committee composition (roster) • Required regulatory authority's(ies') authorization/approval • Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) that are locally obtained • Certification/accreditation for medical/laboratory/technical procedures/tests at start of the study and updates during the conduct of the study for local labs. • Important sponsor and/or TNCC correspondence including: letters, meeting notes, notes of telephone calls • Subject identification list – list of all subjects entered on the study with their sequence number • Subject screening / identification logs, as

	applicable
Original IRB submission including:	• Advertisement(s) to recruit subjects • Informed consent • Any other written information provided to subjects • † Study agent Investigator's Brochure or package insert (if request by IRB for submission) • Case report forms (if request by IRB for submission)
Protocol amendment submission:	• Amended protocol • Amended informed consent • Any other amended written information provided to subjects • Amended advertisement(s) • Amended case report forms (if request by IRB for submission)
All IRB correspondence including:	• Annual renewal/continuing reviews • † Updates to Investigator's Brochure • Adverse event reporting • Acknowledgement of DSMB reports
† Study agent documentation including:	• Receipts sent with shipment of study agent • Study agent accountability logs that reflect log in of study agent shipments • Study agent accountability logs that reflect each time study agent is dispensed • Study agent accountability logs that reflect return or destruction of unused study agent

	• Sample of label(s) attached to investigational product container(s) (what the subject sees) • * Procedures for unbinding trial, if applicable • * Master randomization list, if applicable

The TrialNet site is expected to have source documents to support data points on CRFs:

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

Good standard of practice for source documentation includes:

- Subject identifier information legible on all documents
- All entries are legible and signed by staff
- All entries are made in ink or are typewritten
- Data corrections as follows:
    - Do not ablate incorrect information. Use a strike through so that original information is still legible.
    - Write the date that the document is changed.

- Include initials of the person making the change.
- If corrected information cannot be inserted so it is legible, insert an addendum page with the correction.
- 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.
- Documentation with erasures or use of correction tape/fluid is not acceptable.

RECORD RETENTION

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.

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

- 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.

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.

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.

AUDIT RESULTS

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

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.

IRB Documentation / Study Conduct

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

Informed Consent

Omissions of one or more of the elements required by federal regulations 21 CFR 50.25 / 45 CFR 46.116:	• Statement that the study involves research • Explanation of the purposes of the research • Expected duration of the subject's participation • Description of the procedures to be followed • Identification of any procedures which are experimental • Description of any reasonably foreseeable risks or discomforts to the subject • Description of any benefits to the subject or to others which may reasonably be expected from the research • Disclosure of appropriate alternative procedures or courses of treatment (if any) that may be advantageous to the subject • 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 • 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 • 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 • 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:	• Omissions of multiple risks / side effects as listed in the model informed consent document and/or in subsequent serious adverse event reports • Multiple/cumulative effect of minor problems for a given informed consent
Additional consent form issues:	• Consent form missing • Consent form not signed & dated by subject • No documentation that consent was given and the form was signed by the subject prior to protocol-related studies or procedures • Consent form is missing signatures • Consent form not current IRB-approved version at time of subject enrollment • Consent form not protocol-specific • Consent form doesn't include updates or information as required by IRB • Consent obtained in wrong language

Subject Case Records:

Major violations are assessed as follows:

Eligibility:	• ***Protocol specific eligibility requirements not met*** • Missing source documentation of eligibility requirements
† Treatment administration:	• Incorrect study agent/treatment used • Additional agent used which is not permitted by that protocol • Dose calculated incorrectly • Dose modifications not justified • Treatment doses incorrectly administered, calculated or documented
† Toxicity:	• Failure to assess toxicities and adverse events according to protocol • Grades, types or dates/duration of serious toxicities inaccurately recorded • Toxicities cannot be substantiated • Follow up procedures necessary to assess toxicities not performed • Failure to report toxicity and adverse events
Data quality:	• Recurrent missing source documentation to support data points on CRFs • Protocol specific laboratory or radiology tests not documented • Frequent and recurrent data inaccuracies • Frequent and recurrent errors in submitted data

† *Pharmacy Operations:*

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

FINAL AUDIT CATEGORIES

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

Acceptable assessments do not need a response from the investigator.

Acceptable, Needs Follow-Up assessments require a written response from the TrialNet site Principal Investigator within 4 weeks of the receipt of the audit assessment letter. The 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.

Unacceptable assessments require a written response from the TrialNet site Principal Investigator within 4 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.

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.

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.

- 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 the 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.

- 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.

- 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.

Footnotes:

† Required for investigational agent/ IND interventional/FDA protocols

* Required only if applicable / per protocol

References:

NIH NCI-CTMB Guidelines for monitoring of clinical trials for cooperative groups:
http://ctep.info.nih.gov/monitoring/2006_ctmb_guidelines.pdf

Required Study Documentation: E6 GCP ICH 8.2

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

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

Requirements for Expedited IRB approval (45 CFR 46.110)

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

Informed Consent Requirements: 21 CFR 50.25 and 45 CFR 46.116

14.3. Frequently Asked Questions – Statement of Investigator (Form FDA 1572)

DRAFT GUIDANCE

The TNCC has adopted this guidance into practice and will update pending receipt of final guidance

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 106 1, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact the Patricia M. Beers Block, Good Clinical Practice Program at 301 -827-3340 (Tel).

U.S. Department of Health and Human Services
Food and Drug Administration

July 2008

Additional copies are available at: **http://~~~.fda.gov/oc/gcp/draft.html**

Summary of Contents

This guidance is intended to assist sponsors, institutions, institutional review boards (IRBs) and clinical investigators involved in clinical investigations of investigational drugs and biologics.

This guidance applies to clinical investigations conducted under 2 1 CFR Part 3 12 (Investigational New Drug Applications or IND regulations). It describes how to complete the Statement of Investigator form (Form FDA 1572).

The Food and Drug Administration (FDA or agency) has received a number of questions about the Form FDA 1572. The most frequently asked questions are answered below. If you do not see your question answered here, you may submit it to gcp.questions@,fda.hhs.gov or druginfo@fda.hhhs.gov.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

I. General Questions

1. What is the Statement of Investigator, Form FDA 1572?

The Statement of Investigator, Form FDA 1572 (1 572), is an agreement signed by the investigator to provide certain information to the sponsor and assure that he/she will comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug or biologic. The most recent version of the 1572 is available online at www.fda.**gov/opacom/morechoices/fdaforms/cder.html**

2. Why does this form need to be completed by an investigator?

The 1572 has two purposes:

1) To provide the sponsor with information about the investigator's qualifications and the clinical site that will enable the sponsor to establish and document that the investigator is qualified and the site is an appropriate location at which to conduct the study, and;

2) To inform the investigator of his/her obligations and obtain the investigator's commitment to follow pertinent FDA regulations. Investigators should complete the form as accurately as they can. Investigators should be aware that making a willfully false statement is a criminal offense under 18 U.S.C. 1001. Further, submission of a deliberately false statement to the sponsor or to the agency can be taken into consideration in a disqualification proceeding.

3. When must this form be completed and signed by an investigator?

The sponsor must obtain a completed and signed 1572 before permitting an investigator to begin participation in a clinical study (21 CFR 3 12.53(c)). The investigator should sign the form only after being given enough information to be informed about the study and to understand the commitments described in Block # *9* of the 1572. Having enough information about the study typically means that the investigator has received copies of, has read, and understands the investigator's brochure and the study protocol, and is familiar with the regulations governing the conduct of clinical studies.

The investigator's signature on this form constitutes the investigator's affirmative assertion that he or she is qualified to conduct the study and constitutes the investigator's commitment to abide by FDA regulations in the conduct of the study.

4. Must the investigator be a physician?

The regulations do not require that the investigator be a physician. Sponsors are required to select only investigators qualified by training and experience as appropriate experts to investigate the drug (21 CFR 3 12.53(a)). In the event the clinical investigator is a non-physician, a qualified physician (or dentist, when appropriate) should be listed as a sub-investigator for the trial and should be responsible for all trial-related medical (or dental) decisions (ICH E6 Section 4.3.1; **http://www.fda.gov/cder/guidance/959fnl.pdf).**

5. What are the minimum qualifications of an investigator?

As stated in #4, the regulations require that sponsors select investigators who are qualified by training and experience as appropriate experts to investigate the drug. The regulations do not specify the minimum requirements nor do the regulations specify what qualifications an investigator must have in order to be considered qualified by training and experience to conduct a study. Sponsors have discretion in determining what qualifications will be needed, based on the general recognition that this would include familiarity with human subject protection (HSP) requirements and practices as well as good clinical practice (GCP) standards for the conduct of clinical studies.

6. Does the 1572 need to be submitted to FDA?

No. Although the sponsor is required to collect the 1572 from the investigator, FDA does not require the form to be submitted to the agency. Many sponsors submit the 1572 to FDA, however, because it collects, in one place, information that must be submitted to FDA under 21 CFR 3 12.23(a)(6)(iii)(b).

7. When must a 1572 be updated or a new 1572 completed and signed by the investigator to reflect new or changed information?

If there are changes to information contained on the 1572 (e.g., an IRB address change, the addition of new sub-investigators, discontinuing the use of a clinical lab), the investigator should document the changes in the study records and inform the sponsor of these changes, so that the sponsor can appropriately update the IND. The 1572 itself does not need to be revised and a new
1572 need not be completed and signed by the investigator

8. If a clinical investigation is not conducted under an IND or is for a medical device, must investigators sign a 1572?

No. Under the regulations, a 1572 is only required for studies of investigational drugs and biologics conducted under an IND. It is not required for studies that are not done under an IND, and is not applicable to investigational device studies. Sponsors of device studies must obtain a signed agreement (containing information similar to that requested on the 1572) from each participating investigator, per 21 CFR *8* 12.43(c) **(**[**http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.c?fr-8**12.43](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.c?fr-812.43)).

9. Must a sponsor conduct a foreign clinical study under an IND?

No. A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND.
When a foreign clinical study is conducted under an IND, all FDA IND requirements must be met unless waived (see Question 11 below). When the foreign clinical study is not conducted under an IND, the sponsor must ensure that this study complies with 21 CFR 3 12.120 "Foreign clinical studies not conducted under an IND" if the sponsor intends to submit the study to FDA to support clinical investigations conducted in the United States and/or marketing approval. An application based solely on foreign clinical study data must meet criteria listed in 2 1 CFR3 14.106.

10. Must investigators who conduct studies outside of the United States sign a 15 72?2

If a foreign clinical study is conducted under an IND, then all FDA IND regulations, including the requirement to obtain a signed 1572, must be met. If a study is conducted outside of the U.S. and is not conducted under an IND, then the investigator need not sign a 1572.

11. For foreign clinical studies conducted under an IND, how can an investigator sign the 15 72 when the investigator knows he/she cannot commit to all of the requirements on the form, specifically IRB membership (21 CFR 56.107)?

IRB review and approval is required before a study can be initiated under an IND [21 CFR 56.103(a)]. FDA may waive any of the IRB requirements for specific research activities or for classes of research activities otherwise covered by the IRB regulations [21 CFR 56.1051, but FDA uses the waiver provision only when alternative mechanisms for ensuring protection of the rights and welfare of human subjects are acceptable. The most common circumstance for which FDA receives a waiver request is when a sponsor wishes to conduct a foreign clinical study under an IND. In this case, typically an Independent Ethics Committee (IEC) that operates in accordance with Good Clinical Practice (GCP) is utilized instead of a U.S. IRB. Although its membership and functions for assuring human subject protection are comparable to an IRB, an IEC may not meet all of the IRB requirements contained in 2 1 CFR Part 56.

For foreign studies, an IRB waiver request should contain a description of alternative mechanisms for assuring human subject protection. It would generally be acceptable for a waiver request to state the

intention to use an IEC that complies with GCP (e.g., ICH E6) instead of an IRB that complies with 2 1 CFR Part 56.

The sponsor should submit the waiver request to the IND under which the study will be conducted. The IND will have been submitted to the appropriate review division in either the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER).

The sponsor will be informed by the agency in writing whether the waiver request is denied or granted. If a waiver is granted, the sponsor should have investigators attach a copy of the letter granting the waiver to the signed 1572 in the investigator's record.

12. Must foreign clinical sites in a multinational study that includes domestic sites be conducted under an IND?

No. A multinational study may be comprised of several protocols, some of which are conducted under an IND and others which are not. Investigational drug and biologics studies conducted in the U.S. must be conducted in compliance with the IND requirements contained in 2 1 CFR 3 12, which includes the requirement that investigators sign the 1572. If a study also involves foreign clinical sites, the sponsor may choose, but is not required, to include the foreign clinical sites under the IND. The U.S. sites and any foreign sites included under the IND must follow the protocol that was submitted to the IND and these investigators would be required to sign the 1572. For foreign sites that are not included under the IND, the protocol does not need to be submitted to the IND, and investigators from these foreign sites are not required to sign the 1572. If the intent is to pool the data from U.S. and foreign sites, the protocols would ordinarily be very similar or identical. We recommend that the sponsor discuss plans to pool U.S. and foreign sites with the appropriate FDA review division if the sponsor intends to submit the data from these studies in an application for marketing approval.

Note however, that 2 1 CFR 3 12.320) requires sponsors to promptly review information about the safety of the investigational drug obtained or otherwise received by the sponsor from any source, foreign or domestic. Under 21 CFR 3 12.32(c), sponsors must also notify FDA and all participating investigators in a written IND safety report of any adverse experience associated with the use of the drug that is both serious and unexpected. This means that FDA and all participating investigators under the IND would be informed of such an adverse experience, even if it occurred in a foreign trial not conducted under the IND.

13. How does a sponsor submit information to FDA about a foreign clinical study that was not conducted under an IND?

Under 2 1 CFR 3 12.120, the sponsor can submit information to FDA about a foreign clinical study that was not conducted under an IND when the study is to be utilized to support clinical investigations in the United States and/or marketing approval. When submitting information about a foreign study, it is helpful to clearly identify in the cover letter that the material is being submitted in accordance with 2 1 CFR 3 12.120. Specific instructions on how and what to submit to the agency can be found at 2 1 CFR 3 12.120(b).

14. Should a new form be prepared and signed when the OMB expiration date is reached?

No. There is no need to prepare and sign a new 1572 when the OMB expiration date has been reached. The date on the form refers to the Office of Management and Budget's time frame during which FDA may collect information contained in this form.

15. Does FDA expect a double-sided 1572, or is a two-page documentprinted from the FDA website acceptable?

Either is acceptable; however, FDA recommends that a two-page document be stapled so that there is no question about what form the investigator signed.

16. Is a handwritten form acceptable?

Although the form may be completed by hand, printed copies of the 1572 should be used.

II. Block #I: Name and Address of Investigator

17. How should an investigator's name appear on the 15 72?

Block #1 should contain the investigator's legal name.

18. What address should be entered into Block #I?

The investigator's official address of record should be entered in Block #1 of the 1572.

19. Should co-investigators be listed on the 15 72 in Block #1**?** ***Is it acceptable to have two investigators*****?**

Co-investigators should not be listed in Block #I. The term co-investigator is not defined in FDA regulations. As commonly used, the term is meant to indicate that each co-investigator is fully responsible for fulfilling all of the obligations of an investigator as identified in 21 CFR 3 12.60. Thus under 2 1 CFR 3 12.3(b), each co-investigator is an investigator, and as such must sign a separate 1572. It is acceptable to have more than one investigator at a particular site. This is distinct from a sub-investigator (see #30) whose role in the study is more limited.

III. Block #2: Curriculum Vitae (CV)/Statement of Qualifications

20. What is the purpose of Block #2?

Block #2 requires the investigator to attach the curriculum vitae (CV) or other statement of qualifications, showing the education, training and experience that qualifies the investigator as an expert in the clinical investigation of the drug/biologic for the use under investigation. Information identified in this block and attached to the 1572 enables the sponsor to assess an investigator's qualifications.

21. Does the CV or other statement of qualifications need to be updated during a study?

No. FDA regulations do not require a CV or other statement of qualifications to be updated during a study.

22. Are CVs required to be signed and dated?

No. FDA regulations do not require a CV to be signed and dated. The investigator's signature on the 1572 is sufficient to attest to the accuracy of the CV or other statement of qualifications submitted with the 1572.

IV. Block #3: Research Facilities

23. What address(es) should be entered in Block #3?

The address(es) of the location(s) where the investigation will be conducted and where the test articles will be shipped, if different from the investigator's address of record, should be entered in Block #3.

24. What qualifies as a research facility for Block #3?

Block #3 is intended to identify facilities where study activities will be conducted and study data will be generated or collected. This includes facilities where subjects will be seen and study procedures performed (for example, the location where the test article will be administered, or where physical exams will be performed). Facilities where other important study functions are performed may also be identified in Block #3 (for example, a research laboratory where the test article is prepared or a special storage facility where the test article will be kept).

25. If an investigator sees study subjects at more than one site, should the investigator list all sites on the 15 72?

Yes. The names and addresses of each of the study sites should be identified in Block #3.

26. As a convenience for study subjects, the protocol allows for daily injections to be administered by a registered nurse at each subject's home. Do subjects' home addresses need to be listed in Block #3?

No. Subjects' home addresses do not have to be listed on the 1572. Study records should reflect that the test article was administered at subjects' homes per the protocol.

V. Block #4: Name and Address of Clinical Laboratory Facilities

27. What qualifies as a clinical laboratory facility for Block #4?

Block #4 is intended to identify clinical laboratories or testing facilities directly contributing to or supporting the clinical trial (for example, diagnostic labs performing blood work, imaging centers, cardiology labs, etc.).

28. If a central laboratory is sending samples to its own satellite labs for additional testing, should the satellite labs be identified in Block #4?

It is only necessary to list the central laboratory, provided that the central laboratory can trace the samples to the satellite labs where the tests were performed.

VI. Block #5: Name and address of the Institutional Review Board responsible for the review and approval of the study(ies)

29. Does the IRB reviewing and approving the study have to be at the same location as where the research is conducted?

The regulations permit review of research by IRBs in locations other than where the research is being performed (e.g. independent or non-institutional IRB; use of a cooperative IRB review process; see 21 CFR 56.1 14). Therefore an IRB may review studies that are not performed onsite as long as requirements in 21 CFR Parts 50 and 56 are met.

VII. Block #6: Names of the sub-investigators who will be assist in^ the investigator in the conduct of the investigations

30. Who should be listed as a sub-investigator in Block #6?

FDA's regulation at 21 CFR 3 12.3(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 3 12.53(c)(l)(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)."

The purpose of Block #6 is to capture information about individuals who, as part of an investigative team, will be assisting the investigator and who make a direct and significant contribution to the data. The decision to list an individual in Block #6 depends on his/her level of responsibility (i.e., whether he/she is performing significant study-related duties). In general, if an individual is directly involved in the treatment or evaluation of research subjects, that person should be listed on the 1572. For example, as part of the protocol of a clinical investigation, if each subject needs to visit a specified internist who will perform a full physical to qualify subjects for the study, that internist should be listed in Block #6.

31. Should research nurses, other nurses, residents, fellows, office staff, or other hospital staff be listed in Block #6?

Hospital staff, including nurses, residents, or fellows and office staff who provide ancillary or intermittent care but who do not make a direct and significant contribution to the data do not need to be listed individually. It is not necessary to include in this block a person with only an occasional role in the conduct of the research, e.g., an on-call physician who temporarily dealt with a possible adverse effect or a temporary substitute for any research staff (ICH E3 Section 6**;** http://www.fda.gov/cder/guidance/iche3.pdf).

If a number of staff residents on rotation participate in the study, a general statement regarding their planned participation may be included in Block #6.

32. Should pharmacists or research coordinators be listed in Block #6?

If a pharmacist is merely dispensing tablets and has no responsibility for preparing the test article(s) or evaluating or reporting data relative to the study activities, then it is not necessary to list the pharmacist. On the other hand, if the pharmacist will be compounding, labeling, monitoring and reporting test article compliance data, it would be appropriate to list the pharmacist in Block # 6.

If a research coordinator is performing critical study functions and collecting and evaluating study data, the coordinator should be listed in Block #6**.** If the research coordinator is only transcribing data and maintaining study files, the coordinator does not need to be listed.

33. Is a statement of qualifications required for sub-investigators?

No. The regulations at 2 1 CFR 3 12.53(c) (l)(viii) only require their names to be listed in Block #6 of the 1572.

34. Do individuals who are listed in Block #6 on the 1572 have to submit information about their financial interests?

Yes. Under 2 1 CFR Part 54 (Disclosure of Financial Interests by Clinical Investigators), a person listed or identified as an investigator or sub-investigator who is directly involved in the treatment or evaluation of research subjects must submit financial disclosure information to the sponsor. For purposes of this financial disclosure regulation, the term investigator also includes the spouse and each dependent child of the investigator and sub-investigator. (21CFR 54.2(d) and 54.4).

As further explained in the FDA Guidance for Industry Financial Disclosure by Clinical Investigators (http://www.fda.gov/oc/guidance/financialdis.html), for drugs and biological products, clinical investigator means the individual(s) who actually conduct(s) and take(s) responsibility for an investigation, i.e., under whose immediate direction the drug or biologic is administered or dispensed to a subject or who is directly involved in the evaluation of research subjects. Where an investigation is directed by more than one person at a site, there may be more than one investigator who must report. The terms investigators and sub-investigators include persons who fit any of these criteria: sign the Form FDA 1572, are identified as an investigator in initial submissions or protocol amendments under an IND, or are identified as an investigator in the NDAIBLA. For studies not conducted under an IND, the sponsor will need to identify in Form FDA 3454 and/or Form FDA 3455 the names of investigators and sub-investigators they consider covered by 21 CFR Part 54. We expect that there will be at least one such person at each clinical site. If, however, there are other persons who are responsible for a study at a site, those persons should also be included as investigators.

The definition of "clinical investigator" in 21 CFR Part 54 is intended to identify the individuals who should be considered investigators for purposes of reporting under the rule, generally, the people taking responsibility for the study at a given study site. For drugs, biological products and devices, it should be noted that hospital staff, including nurses, residents, or fellows and office staff who provide ancillary or intermittent care, but who do not make direct and significant contribution to the data, are not meant to be included under the definition of clinical investigator.

14.4. Documentation of Screening Consent Process

Study Name _____ Protocol # _____

Patient # _____ Patient Initials _____

___ Records reviewed for inclusion / exclusion criteria
___ Patient / subject was seen by delegation of principal investigator
___ Consents reviewed with subject
___ HIPAA form reviewed with subject
___ All questions / concerns were answered / addressed
___ Patient agreed to participate in study
___ Consents signed and dated
___ HIPAA form signed and dated (if applicable)
___ Copy of signed consent was given to patient/subject
___ Above process completed before any procedures for protocol were done

_____ _____
Signature of Person Obtaining Consent Date

14.5. Documentation of Volunteer Understanding Assessment Review

Study Name _____ Protocol # _____

Patient # _____ Patient Initials _____

___ Volunteer Assessment answers reviewed/checked against answer key

___ Wrong answers reviewed with participant (if not applicable please put “N/A”)

___ All questions / concerns were answered / addressed

___ Participant understands study

___ If participant does not understand, site reviewed study with participant again (if not applicable please put “N/A”)

___ Above process completed before any procedures for protocol were done

_____ _____

Signature of Person Obtaining Consent Date

14.6. Volunteer Survey Answer KEY

Type 1 Diabetes TrialNet

Anti IL-1Beta (Canakinumab) Study
VOLUNTEER UNDERSTANDING SURVEY

Screening ID: _ _ _ _ _ - _ _ Participant Letters: _ _ _

The Canakinumab Volunteer Understanding Survey is based on the information that has been presented to you regarding this clinical research study. All of the questions are based on this information. The purpose of this survey is to be sure you know the details of this clinical research study before you agree to be part of it. After you have finished the survey, the research study team will go over the answers with you. The research study team will be sure to discuss any answers that were incorrect, because it is important to us that you understand the study.

Date that survey was completed: _____ / _____ / _____ _ (DAY / MONTH / YEAR)

Put an "X" or a check in the box next to the best answer(s) to each question.
You may take as much time as you want to answer these questions.

1. The reason I am being asked to be in this research study is:
   - ☐ 1 I have recently been diagnosed with Type 1 diabetes
   - ☐ 2 I am at high risk for developing Type 1 diabetes
   - ☐ 3 I have recently been diagnosed with Type 2 diabetes
   - ☐ 4 I do not know why I am being asked to be in this research study

2. The reason for doing this research study is to see:
   - ☐ 1 If giving experimental treatment *before* Type 1 diabetes starts will keep a person from getting Type 1 diabetes
   - ☐ 2 If giving experimental treatment within 12 weeks *after* Type 1 diabetes starts will help my insulin producing cells work longer by keeping them from being destroyed
   - ☐ 3 If testing my blood sugar more frequently will keep my Type 1 diabetes under control
   - ☐ 4 I do not know a reason for doing this study

3. If I decide to be in this research study, I will come to a study site for:
   - ☐ 1 One year
   - ☐ 2 Two years
   - ☐ 3 At least two years and possibly up to four years
   - ☐ 4 I do not know

4. If I decide to be in this research study, I will receive subcutaneous injections of canakinumab or placebo:
   - ☐ 1 monthly for one year
   - ☐ 2 monthly for two years
   - ☐ 3 Every 6 months for 2 years
   - ☐ 4 I do not know how many injections I will receive

5. If I agree to be in this research study, I will have to *(check all that apply)*:
   - ☐ 1 Let my study team know about any health problems that occur whether or not I think they are important because I am in the study
   - ☐ 2 Stay in the treatment group I am assigned to until the research study ends
   - ☐ 3 Keep all appointments at the clinic
   - ☐ 4 I do not know

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6. I will need to have visits to the study site *(check all that apply)*:

- ☐ 1 Monthly the first year
- ☐ 2 Every six months the second year
- ☐ 3 If I continue to make insulin at the end of two years, I will have additional visits every 6 months for up to 2 more years
- ☐ 4 I don't know

7. My assignment to the treatment group or the control group will be random. This means:

- ☐ 1 I will have a 2 out of 3 chance of getting the medicine and a 1 out of 3 chance of getting the placebo (A placebo is a "pretend" medicine that looks like the real medicine, but is not active)
- ☐ 2 I can choose which group I want to be in
- ☐ 3 The doctor decides which group I will be in
- ☐ 4 I will be in the group that is best for me to be in
- ☐ 5 I am not sure of how I will be assigned to a group

8. My participation in this research study is voluntary. This means:

- ☐ 1 I must stay in this research study until the entire research study ends
- ☐ 2 I can choose to not be in this research study or to stop being in this research study at any time, but I will not get as good of diabetes care if I do
- ☐ 3 I can choose to not be in this research study or to stop being in this research study at any time and no one will be mad at me, I will still receive the same diabetes care
- ☐ 4 I do not know what voluntary means

9. The risks of being in this research study may include *(check all that apply)*:

- ☐ 1 There are no risks to being in this research study
- ☐ 2 Infections (i.e., respiratory and urinary tract)
- ☐ 3 Tenderness at the injection site
- ☐ 4 Hair loss

10. The guaranteed benefits of being in this research study include *(check all that apply)*:

- ☐ 1 I will not need to take insulin anymore
- ☐ 2 There are no guaranteed benefits to being in this research study
- ☐ 3 I will not need to check my blood sugar as frequently
- ☐ 4 I will no longer have diabetes

11. If I decide to be in this research study, I will have to pay for *(check all that apply)*:

- ☐ 1 The procedures and tests that will be required
- ☐ 2 The study medicines I will be taking
- ☐ 3 My diabetes treatment supplies (e.g., insulin, needles, insulin pump supplies)
- ☐ 4 I do not know what I will have to pay for

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12. Which statements are true regarding routine vaccinations or immunizations while I am in the research study? *(Check all that apply)*

- ☐ 1 I should not have any live vaccinations or immunizations for one month prior to enrolling into the study
- ☐ 2 I should not have any live vaccinations or immunizations for 15 months after enrolling into the study (12 months during treatment and 3 months after completing the treatment phase)
- ☐ 4 It is OK to have any type of vaccinations or immunizations during the study
- ☐ 5 I do not know if I can have vaccinations or immunizations during the study.

13. If I decide to be in this research study, my diabetes management plan will require that I *(check all that apply)*:

- ☐ 1 Take insulin injections only every other day and test my blood sugars when I don't feel well
- ☐ 2 Report my insulin use (i.e., number of injections, type of insulin, use of an insulin pump) and blood sugar results to the study site every two weeks
- ☐ 3 Use an insulin pump and test my blood sugars before bedtime only
- ☐ 4 Check and record my blood sugars at least four times a day
- ☐ 5 I do not know how often I will need to take insulin or test my blood sugars

14. If I am in the study I will not be required to come for MMTT testing one week after the 6 month injection. This visit is optional.

- ☐ 1 True
- ☐ 2 False

15. As part of this study, I will receive immunizations for (*check all that apply*):

- ☐ 1 Tetanus
- ☐ 2 Pneumonia
- ☐ 3 Flu
- ☐ 4 I do not know which immunizations I will receive

Female Participants of reproductive potential only:

16. If I agree to be in this research study, I must agree to use effective birth control for the first 15 months (12 months during the treatment phase plus 3 months following last injection) while I am participating in the study.

- ☐ 1 True
- ☐ 2 False

END OF SURVEY

15. Appendix A: Preparation for a MMTT

Sample Menu

The menu below contains 150 grams of carbohydrate. In order to prepare for your test, please consume a minimum of 150 grams of carbohydrate per day for the 3 days prior to the test. You must be fasting on the morning of the test.

The number of grams of carbohydrates is listed in parentheses for each serving of food. You may substitute any items from the lists below; and you can eat more than this if you wish. Add as many servings of meats or vegetables as desired; the menu below is only an example. Be sure to drink plenty of water in preparation for the test.

Breakfast
4 oz. orange juice (15)
4 oz. milk (whole, low fat, 1%, or non-fat) (6)
3/4 cup dry cereal (15)

Snack
1 medium apple (20)

Lunch
Sandwich with 2 slices of bread (30) and any filling
1 banana (20)

Dinner
1 serving of meat, fish or poultry (0)
1 medium size potato (20) with topping
1 serving of vegetables (5)
1/2 cup canned fruit (15)

Snack
2 cups popcorn (10)

10 grams	15 grams	20 grams	30 grams
10 grapes	½ cup cooked cereal	1 medium apple	2 toaster waffles
1 cup strawberries	6 saltines	1 hamburger bun	1 cup pasta
8 oz. tomato juice	4 oz. fruit juice	1 small corn on the cob	1 small bagel
1 plum	1 slice angel food	9 animal crackers	1 cup chicken noodle soup
1 Fig Newton	½ pita	3 dates	1 piece plain cake
4 vanilla wafers	2 tbsp. raisins	½ cup rice	
4 Ritz crackers			

Because a large number of factors may affect the MMTT, care must be taken to properly prepare participants for the test.

Dietary guidelines:

- High (at least 150 grams) CHO diet for at least 3 days prior to the test
- Fasting after 10:00pm the night before the test.

- 10 hr abstinence from coffee, tea, sodas, caffeine containing drinks, cigarettes, alcohol, chewing gum , vigorous exercise
- Water consumption is encouraged, especially for young children

Other guidelines:

- No consumption of over the counter medications during the fasting period.
- Inform study staff if taking any prescription medications that you, or your child, must take, 3 days before the test so that appropriate directions can be given on how to deal with this medication before the test.
- Not participate in vigorous exercise during the 10 hours before the test.

If the participant has not consumed sufficient dietary carbohydrate before the test, the insulin secretory response to the mixed meal stimulus may not be as great as it should be (*may not be accurate)* and the test results may be unreliable. Therefore, the participant must consume a high carbohydrate diet, with ≥ 150 grams carbohydrate per day, for a minimum of three full days prior to testing.

- The test should be **rescheduled** if the participant has a blood glucose (measured on his/her home meter) **less than 70 mg/dl (3.85 mmol/L) or greater than 200 mg/dl**. **(11.1 mmol/L)**
- The test must begin between the hours of **7(AM) and 10AM**.
- The participant should remain seated during the performance of the test.
- The test is started in the morning after a night's sleep (*a full night's rest)*. Participants may not work during the night preceding the morning of the test.
- The test should be postponed for at least one week after any intercurrent infectious illness, surgery or other stress.

Insulin Guidelines

- Long-acting insulin can be administered the day before the test is scheduled.
- Corrective insulin (Humalog (H) and NovoLog) can be administered up to two hours before the test.
- Regular (R) insulin can be administered up to six hours before the test.
- Participants on insulin pumps (continuous insulin infusions (CSII)) should continue with the normal basal rate, but a Humalog (H) or NovoLog bolus may be added up to 2 hours prior to the test, and Regular (R) bolus up to 6 hours prior to the test.

15.1. MMTT Administration Eligibility ☑ Checklist**

☐	Subject fasted (did not eat) after 10:00pm the night before the test up until the start of the test *__Includes:__ *Subject avoided all food, drink (EXCEPTION: water)*
☐	Followed allowable insulin guidelines: • Long-acting insulin can be administered the day before the test is scheduled. • Corrective insulin (Humalog (H) and NovoLog) can be administered up to two hours before the test. • Regular (R) insulin can be administered up to six hours before the test. • Participants on insulin pumps (continuous insulin infusions (CSII)) should continue with the normal basal rate, but a Humalog (H) or NovoLog bolus may be added up to 2 hours prior to the test, and Regular (R) bolus up to 6 hours prior to the test.
☐	Subject abstained from consuming *coffee, tea, sodas, caffeine containing drinks, cigarettes, alcohol, or chewing gum* during the fasting period (10 hours before the test)
☐	Subject refrained from vigorous exercise during the fasting period (10 hours before the test).
☐	Subject refrained from working during the night preceding the morning of the test.
☐	PI reviewed medication list including over the counter meds to determine whether ok to proceed with test. Note, PI may contact TNCC CRA, Study Chair, or TN Vice-Chair if he/she is uncertain about whether MMTT should be performed.
☐	If subject has had an illness, surgery, or infection the PI has evaluated the subject and determined whether the test should be done. Note, the PI may contact the TNCC CRA, Study Chair, or TN Vice-Chair if he/she is uncertain about whether the MMTT should be performed
☐	Subject ate a high carbohydrate diet (at least 150 grams) (*Sample Menu* - see Appendix A, Section 13, pg 150 of the MOO for details) for 3 days prior to testing.
☐	If subject has had an illness, surgery, or infection the PI has evaluated the subject and contacted the TNCC CRA, Study Chair, and Dr. Carla Greenbaum to determine whether test should be done
☐	Subject is not pregnant, does not have any chronic illness such as cancer, nephritic syndrome, active hepatitis, or some other life threatening illness.
☐	At the start of MMTT the subject's blood glucose was greater than or equal to 70 mg/dl but less than or equal to 200 mg/dl (between 70 mg/dl – 200 mg/dl)
☐	MMTT started after 7AM or before 10 AM (i.e. -10 min sample was drawn after 7AM or before 10AM)

***If any items are not checked (including "not applicable" where appropriate) or you have questions or concerns please contact your protocol CRA at the TNCC before you move forward.*

14. Appendix B

Participant ID: _____ Local Code: _____ FTL: _____ Study: TN___ ___

A. GENERAL INFORMATION

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

B. GENERAL SUBJECT INFORMATION

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

C. ELIGIBILITY ISSUE DETAILS

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

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

D. RELEVANT INFORMATION FROM STUDY DOCUMENTS

TNCC USE ONLY

1. Eligibility reviewed? Y N

IF YES,

a. Date of review: __ __ / __ __ / __ __ __ __ (MM DD YYYY)

b. Reviewer ☐ 1 TNCC ☐ 2 Committee Chair ☐ 3 Full Committee

c. Eligibility decision: ☐ 1 Eligible ☐ 2 Not Eligible

If NO,

a. Reason not reviewed:

2. Comments:

15. Appendix C

_____
Site Name
The following is an internal checklist for use by clinical sites that covers the basic steps for initiating the TNXX Trial. The checklist covers the following general areas:

- ☑ Providing TNCC with contact and other information
- ☑ Training and Certification
- ☑ IRB approval and other compliance documents
- ☑ Preparing for study start-up

Item	Completed	Date/Initials
Getting Started		
Confirm site interest in participation and determine a timeline for implementation with TNCC	☐	
Complete Form FDA 1572 and Financial Disclosure Form FDA 3455 (if applicable)	☐	
Submit updated Site Delegation Log to TNCC ensuring that all individuals at your site who will be assisting in the conduct of the study are listed on the SDL with the appropriate study roles specified	☐	
Submit New User or Contact Correction form to the TNCC for new TrialNet Members, Current TrialNet Members with corrections to contact information, and for TrialNet Members who need to be removed or are inactive	☐	
Complete EMINENT Client Contact Form which provides the TNCC and EMINENT with contact and shipping information for local pharmacy or alternate location that will receive shipment of study medications (*Note: The name of a contact at the pharmacy MUST be provided and the person ordering study drug must be a licensed medical professional)	☐	
Confirm access to 2°C to 8°C (36°F to 46°F) degree refrigerator in the pharmacy for storage of study medication	☐	
Confirm access to -20°C freezer for storage of frozen samples until shipment	☐	
Confirm access to -4°C refrigerator for storage of samples until shipment	☐	
Confirm access to area to hold room temperature samples until shipment	☐	
Training and Certification		
Review current protocol, study procedures, and other study documents	☐	
Train at least one person at your site on the online data capture system (protocol manager) and certify for all required study procedures and tests	☐	
Ensure that staff who will be assisting with all aspects of the study are appropriately trained to do so •	☐	
Ensure that each individual listed on the site delegation log has completed a Duality of Interest Form (this can be completed online)	☐	

SITE INITIATION CHECKLIST

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17JUL2009

IRB Approval		
Prepare IRB submission and submit to local IRB (protocol, consents, assents, IB, patient handbook, etc…)	☐	
Inform TNCC when protocol has been submitted to local IRB and date of review	☐	
Respond to any issues raised by the local IRB (TNCC and Chairman's Office can assist you with this)	☐	
Send approval letter and approved consents that reflect the appropriate version number, date of the protocol, and approval period to the TNCC (*Note: If your IRB does not stamp consents or specify approval periods on IRB approved documentation your IRB's policy on version control is required)	☐	
Implementation		
Initiate protocol activities including registration, obtaining consent, and screening, after activation letter is received from TNCC.	☐	
Review laboratory supplies at the site and order what the site needs for the TNXX Study using the Supply Ordering System (SOS)	☐	
Review shipping procedures for TrialNet Laboratory samples and forms	☐	
Review protocol and procedures with lab coordinator to ensure site is prepared for mechanistic sample collections as well as all other collections	☐	
The TNCC completes and sends an Agent Request Form to EMINENT requesting two kits for the site (in TNXX Pharmacy Manual of Operations). Once a site is activated for the protocol TNXX by the TNCC, the TNCC will email a scanned copy of the order to the Trial Coordinator at the site.	☐	

_____	_____	_____
Printed Name	*Signature*	*Date*
_____	_____	_____
Printed Name	*Signature*	*Date*

16. Appendix D: Glucose Log Template

Week of _____-_____

Long acting insulin/Basal Rate: Short Acting Insulin: Correction factor: Insulin/carb ratio:	Fax or e-mail weekly to: Fax: Email:

Day of the week / date		BREAKFAST		LUNCH		DINNER		PM Snack		BEDTIME	NIGHT	COMMENTS
		PRE	POST	PRE	POST	PRE	POST	PRE	POST			
MONDAY	TIME											
	BG											
	CARB											
	INSUL											
TUESDAY	TIME											
	BG											
	CARB											
	INSUL											
WED	TIME											
	BG											
	CARB											
	INSUL											
THURS	TIME											
	BG											
	CARB											
	INSUL											
FRIDAY	TIME											
	BG											
	CARB											
	INSUL											
SAT	TIME											
	BG											
	CARB											
	INSUL											
SUNDAY	TIME											
	BG											
	CARB											
	INSUL											

17. Appendix E: PID/LID Screening Log for TN14 Anti IL-1Beta Study

Study: TN14 Anti IL-1Beta Site ID: Site Name:						
Local ID	**Participant ID**	**FTL**	**Date Screened**	**100 Day Window Closes**	**MMTT Window Closes**	**Comments**

18. Appendix D: Adverse Event Log

SITE NAME:		21SEP2009 Version 1.0 Page 159 of 1
Participant ID: _ _ _ _ _ _	Local ID: ____________	Participant Letters: __ __ __

Description of Adverse Event	Start Date dd/mm/yyyy	Stop Date dd/mm/yyyy	Type of AE	Serious* Criteria		Intensity/ Grade	Attribution	Action Taken	Outcome	Date Sent to IRB	PI Initials & Date
	__/__/__	__/__/__	☐ Expected ☐ Unexpected	☐ Yes	☐ No	☐ Mild/1 ☐ Moderate/2 ☐ Severe/3 ☐ Life-threatening or Disabling/4 ☐ Death/5	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	☐ None ☐ Hospitalized ☐ Other : __________ __________	☐Recovered ☐Improved ☐Ongoing ☐Death ☐Unknown	/ / ☐ N/A	
	__/__/__	__/__/__	☐ Expected ☐ Unexpected	☐ Yes	☐ No	☐ Mild/1 ☐ Moderate/2 ☐ Severe/3 ☐ Life-threatening or Disabling/4 ☐ Death/5	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	☐ None ☐ Hospitalized ☐ Other : __________ __________	☐Recovered ☐Improved ☐Ongoing ☐Death ☐Unknown	/ / ☐ N/A	
	__/__/__	__/__/__	☐ Expected ☐ Unexpected	☐ Yes	☐ No	☐ Mild/1 ☐ Moderate/2 ☐ Severe/3 ☐ Life-threatening or Disabling/4 ☐ Death/5	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	☐ None ☐ Hospitalized ☐ Other : __________ __________	☐Recovered ☐Improved ☐Ongoing ☐Death ☐Unknown	/ / ☐ N/A	
	__/__/__	__/__/__	☐ Expected ☐ Unexpected	☐ Yes	☐ No	☐ Mild/1 ☐ Moderate/2 ☐ Severe/3 ☐ Life-threatening or Disabling/4 ☐ Death/5	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	☐ None ☐ Hospitalized ☐ Other : __________ __________	☐Recovered ☐Improved ☐Ongoing ☐Death ☐Unknown	/ / ☐ N/A	
	__/__/__	__/__/__	☐ Expected ☐ Unexpected	☐ Yes	☐ No	☐ Mild/1 ☐ Moderate/2 ☐ Severe/3 ☐ Life-threatening or Disabling/4 ☐ Death/5	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	☐ None ☐ Hospitalized ☐ Other : __________ __________	☐Recovered ☐Improved ☐Ongoing ☐Death ☐Unknown	/ / ☐ N/A	
	__/__/__	__/__/__	☐ Expected ☐ Unexpected	☐ Yes	☐ No	☐ Mild/1 ☐ Moderate/2 ☐ Severe/3 ☐ Life-threatening or Disabling/4 ☐ Death/5	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	☐ None ☐ Hospitalized ☐ Other : __________ __________	☐Recovered ☐Improved ☐Ongoing ☐Death ☐Unknown	/ / ☐ N/A	

19. Appendix E: Concomitant Medication Log

SITE NAME:

Participant ID: _ _ _ _ _ _ Local ID: _____ Participant Letters: __ __ __

Assess Date	Assessed By (Signature)	Medication	Dose	Units (mg, ml)	Frequency (BID, TID)	Interval (QD, QOD)	Route (PO, IV, etc.)	Indication	Checked Against Drug Interaction List?	Start Date	Continuing?	If no, Stop Date
									O Y O N		O Y O N	
									O Y O N		O Y O N	
									O Y O N		O Y O N	
									O Y O N		O Y O N	
									O Y O N		O Y O N	
									O Y O N		O Y O N	
									O Y O N		O Y O N	
									O Y O N		O Y O N	
									O Y O N		O Y O N	
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									O Y O N		O Y O N	
									O Y O N		O Y O N	
									O Y O N		O Y O N	
									O Y O N		O Y O N	
									O Y O N		O Y O N	
									O Y O N		O Y O N	
									O Y O N		O Y O N	

20. Appendix F: Deviation Log

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SITE NAME

Participant ID: _ _ _ _ _ _ Local ID: ____________ Participant Letters: __ __ __

Deviation Documented by	**Description of Protocol Deviation**	**Deviation dd/mm/yyyy**	**Action Taken**	**Date IRB Notified (if applicable)**		**PI Notified**	***(If PI Notified)* PI Initials**
		__ __/__ __ __ /__ __ __ __		__ __/__ __ __ /__ __ __ __	☐ N/A	○ Y ○ N	
		__ __/__ __ __ /__ __ __ __		__ __/__ __ __ /__ __ __ __	☐ N/A	○ Y ○ N	
		__ __/__ __ __ /__ __ __ __		__ __/__ __ __ /__ __ __ __	☐ N/A	○ Y ○ N	
		__ __/__ __ __ /__ __ __ __		__ __/__ __ __ /__ __ __ __	☐ N/A	○ Y ○ N	
		__ __/__ __ __ /__ __ __ __		__ __/__ __ __ /__ __ __ __	☐ N/A	○ Y ○ N	
		__ __/__ __ __ /__ __ __ __		__ __/__ __ __ /__ __ __ __	☐ N/A	○ Y ○ N	
		__ __/__ __ __ /__ __ __ __		__ __/__ __ __ /__ __ __ __	☐ N/A	○ Y ○ N	
		__ __/__ __ __ /__ __ __ __		__ __/__ __ __ /__ __ __ __	☐ N/A	○ Y ○ N	

Questions & Answers

2010-2011 Flu Season

What sort of flu season is expected this year?

Flu seasons are unpredictable in a number of ways. Although epidemics of flu happen every year, the timing, severity, and length of the epidemic depends on many factors, including what influenza viruses are spreading and whether they match the viruses in the vaccine. Last flu season (2009-2010) saw the emergence of the 2009 H1N1 influenza virus (previously called "novel H1N1" or "swine flu"). This virus caused the first influenza pandemic (global outbreak of disease caused by a new flu virus) in more than 40 years. While not certain, it is likely that 2009 H1N1 viruses will continue to spread along with seasonal viruses in the U.S. during the 2010-2011 flu season.

Will new strains of flu circulate this season?

Flu viruses are constantly changing so it's not unusual for new flu virus strains to appear each year. For more information about how flu viruses change, visit "How the Flu Virus Can Change." While not certain, it is likely that 2009 H1N1 viruses and seasonal viruses will cause illness in the U.S. during the 2010-2011 flu season.

When will flu activity begin and when will it peak?

The timing of flu is very unpredictable and can vary from season to season. Flu activity most commonly peaks in the U.S. in January or February. However, seasonal flu activity can occur as late as May.

What should I do to prepare for this flu season?

CDC recommends a yearly flu vaccine for everyone as the first and most important step in protecting against this serious disease. While there are many different flu viruses, the flu vaccine is designed to protect against the three main flu strains that research indicates will cause the most illness during the flu season. The 2010-2011 flu vaccine will protect against three different flu viruses: an H3N2 virus, an influenza B virus and the H1N1 virus that caused so much illness last season. Getting the flu vaccine soon after it becomes available each year is always a good idea, and the protection you get from vaccination will last throughout the flu season.

How effective is the flu vaccine?

The effectiveness of the vaccine can vary and depends in part on the match between the viruses in the vaccine and flu viruses that are circulating in the community. If these are closely matched, vaccine effectiveness (VE) is higher. If they are not closely matched, VE can be reduced. During well-matched years, clinical trials have shown VE between 70%

and 90% among healthy adults. For more information about vaccine effectiveness, visit "How Well Does the Seasonal Flu Vaccine Work?"

Will this season's vaccine be a good match for circulating viruses?

It's not possible to predict with certainty which flu viruses will predominate during a given season. Flu viruses are constantly changing (called drift) – they can change from one season to the next or they can even change within the course of one flu season. Experts must pick which viruses to include in the vaccine many months in advance in order for vaccine to be produced and delivered on time. (For more information about the vaccine virus selection process visit "Selecting the Viruses in the Influenza (Flu) Vaccine.") Because of these factors, there is always the possibility of a less than optimal match between circulating viruses and the viruses in the vaccine.

How do we know if there is a good match between the vaccine viruses and those causing illness?

Over the course of a flu season CDC studies samples of flu viruses circulating during that season to evaluate how close a match there is between viruses in the vaccine and circulating viruses. In addition, CDC conducts vaccine effectiveness studies to determine how well the vaccine protects against illness. However, it's important to remember that even during seasons when the vaccine is not optimally matched to predominant circulating viruses, CDC and other experts continue to recommend flu vaccine as the best way to protect against the flu.

Can the vaccine provide protection even if the vaccine is not a "good" match?

Yes, antibodies made in response to vaccination with one strain of flu viruses can provide protection against different, but related strains. A less than ideal match may result in reduced vaccine effectiveness against the variant viruses, but it can still provide some protection against influenza illness. In addition, it's important to remember that the flu vaccine contains three virus strains so that even when there is a less than ideal match or lower effectiveness against one strain, the vaccine may protect against the other two viruses. For these reasons, even during seasons when there is a less than ideal match, CDC continues to recommend flu vaccination. This is particularly important for people at high risk for serious flu complications, and their close contacts.

In what years was there a good match between the vaccine and the circulating viruses?

In recent years the match between the vaccine viruses and those identified during the flu season has usually been good. In 16 of the last 20 U.S. influenza seasons the viruses in the influenza vaccine have been well matched to the predominant circulating viruses. Since 1990, there has only been one season (1997-98) when there was very low cross-reaction between the viruses in the vaccine and the predominate circulating virus, and

three seasons (1992-93, 2003-04, and 2007-08) when there was low cross-reaction. In response to the emergence of the 2009 H1N1 virus last season (2009-2010), a new flu vaccine was developed which was a good match to the new virus.

What is CDC doing to monitor vaccine effectiveness for the 2010-2011 season?

CDC carries out and collaborates with other partners within and outside CDC to assess the effectiveness of flu vaccines. During the 2010-2011 season, CDC is planning multiple studies on the effectiveness of influenza vaccine. These studies will measure vaccine effectiveness in preventing laboratory confirmed influenza in older people and in children.

What actions can I take to protect myself and my family against the flu this season?

CDC recommends a yearly flu vaccine as the first and most important step in protecting against this serious disease. While there are many different flu viruses, the flu vaccine protects against the three main flu strains that research indicates will cause the most illness during the flu season. For information about vaccine supply this season, please visit http://www.cdc.gov/flu/about/qa/vaxsupply.htm.

In addition, you can take everyday preventive steps like staying away from sick people and washing your hands to reduce the spread of germs. If you are sick with flu, stay home from work or school to prevent spreading influenza to others..

Is there treatment for the flu?

Yes. If you get sick, there are drugs that can treat flu illness. They are called antiviral drugs and they can make your illness milder and make you feel better faster. For more information about antiviral drugs, visit http://www.cdc.gov/flu/antivirals/index.htm.

What is antiviral resistance?

Antiviral resistance means that a virus has changed in such a way that the antiviral drug is less effective in treating or preventing illness. Samples of viruses collected from around the United States and worldwide are studied to determine if they are resistant to any of the four FDA-approved influenza antiviral drugs.

What is CDC doing to monitor antiviral resistance in the United States during the 2010-11 season?

CDC routinely collects viruses through a domestic and global surveillance system to monitor for changes in influenza viruses. CDC will continue ongoing surveillance and testing of influenza viruses. Additionally, CDC is working with the state public health departments and the World Health Organization to collect additional information on

antiviral resistance in the United States and worldwide. The information collected will assist in making informed public health policy recommendations.

Key Facts About Influenza (Flu) & Flu Vaccine

What is Influenza (Also Called Flu)?

The flu is a contagious respiratory illness caused by influenza viruses. It can cause mild to severe illness, and at times can lead to death. The best way to prevent the flu is by getting a flu **vaccine** each year.

Symptoms of Flu

People who have the flu often feel some or all of these symptoms:

- fever* or feeling feverish/chills
- cough
- sore throat
- runny or stuffy nose
- muscle or body aches
- headaches
- fatigue (very tired)
- Some people may have vomiting and diarrhea, though this is more common in children than adults.

***It's important to note that not everyone with flu will have a fever.**

How Flu Spreads

Most experts believe that flu viruses spread mainly by droplets made when people with flu cough, sneeze or talk. These droplets can land in the mouths or noses of people who are nearby. Less often, a person might also get flu by touching a surface or object that has flu virus on it and then touching their own mouth, eyes or nose.

Period of Contagiousness

You may be able to pass on the flu to someone else before you know you are sick, as well as while you are sick. Most healthy adults may be able to infect others beginning 1 day **before** symptoms develop and up to 5-7 days **after** becoming sick. Some people, especially children and people with weakened immune systems, might be able to infect others for an even longer time.

How Serious is the Flu?

Flu is unpredictable and how severe it is can vary widely from one season to the next depending on many things, including:

- what flu viruses are spreading,
- how much flu vaccine is available
- when vaccine is available
- how many people get vaccinated, and
- how well the flu vaccine is matched to flu viruses that are causing illness.

Certain people are at greater risk for serious complications if they get the flu. This includes older people, young children, pregnant women and people with certain health conditions (such as asthma, diabetes, or heart disease).

One study found that during the 1990s, flu-related deaths ranged from an estimated 17,000 during the mildest season to 52,000 during the most severe season (36,000 average). Studies going back to 1976 have found that flu-related deaths ranged from a low of 4,700 to a high of 56,600 (average 25,500). During a regular flu season, about 90 percent of deaths occur in people 65 years and older.

During 2009-2010, a new and very different flu virus (called 2009 H1N1) spread worldwide causing the first flu pandemic in more than 40 years. It is estimated that the 2009 H1N1 pandemic resulted in more than 12,000 flu-related deaths in the U.S. In contrast to seasonal flu, nearly 90 percent of the deaths occurred among people younger than 65 years of age.

Complications of Flu

Complications of flu can include bacterial pneumonia, ear infections, sinus infections, dehydration, and worsening of chronic medical conditions, such as congestive heart failure, asthma, or diabetes.

Preventing Seasonal Flu: Get Vaccinated

The single best way to prevent the flu is to get a flu vaccine each season. There are two types of flu vaccines:

- **The "flu shot"**–an inactivated vaccine (containing killed virus) that is given with a needle. The seasonal flu shot is approved for use in people 6 months of age and older, including healthy people, people with chronic medical conditions and pregnant women.
- • **The nasal–spray flu vaccine** –a vaccine made with live, weakened flu viruses that do not cause the flu (sometimes called LAIV for "Live Attenuated Influenza Vaccine"). LAIV is approved for use in healthy* people 2-49 years of age who are not pregnant.

About two weeks after vaccination, antibodies develop that protect against influenza virus infection. Flu vaccines will not protect against flu-like illnesses caused by non-influenza viruses.

The seasonal flu vaccine protects against the three influenza viruses that research suggests will be most common. The 2010-2011 flu vaccine will protect against 2009 H1N1, and two other influenza viruses (an H3N2 virus and an influenza B virus).

When to Get Vaccinated Against Seasonal Flu

Yearly flu vaccination should begin in September, or as soon as vaccine is available, and continue throughout the flu season which can last as late as May. This is because the timing and duration of flu seasons vary. While flu season can begin early as October, most of the time seasonal flu activity peaks in January or later.

Who Should Get Vaccinated?

On February 24, 2010 vaccine experts voted that everyone 6 months and older should get a flu vaccine each year starting with the 2010-2011 influenza season. CDC's Advisory Committee on Immunization Practices (ACIP) voted for "universal" flu vaccination in the U.S. to expand protection against the flu to more people. While everyone should get a flu vaccine each flu season, it's especially important that certain people get vaccinated either because they are at high risk of having serious flu-related complications or because they live with or care for people at high risk for developing flu-related complications.

Who is at Higher Risk for Developing Flu-Related Complications?

- Children younger than 5, but especially children younger than 2 years old,
- Adults 65 years of age and older
- Pregnant women, and,
- People who have medical conditions including:
    - Asthma (even if it's controlled or mild)
    - Neurological and neurodevelopmental conditions [including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy, or spinal cord injury].
    - Chronic lung disease (such as chronic obstructive pulmonary disease [COPD] and cystic fibrosis)
    - Heart disease (such as congenital heart disease, congestive heart failure and coronary artery disease)
    - Blood disorders (such as sickle cell disease)

    - Endocrine disorders (such as diabetes mellitus)
    - Kidney disorders
    - Liver disorders
    - Metabolic disorders (such as inherited metabolic disorders and mitochondrial disorders)
    - Weakened immune system due to disease or medication (such as people with HIV or AIDS, or cancer, or those on chronic steroids)
    - People younger than 19 years of age who are receiving long-term aspirin therapy
    - People with Chronic Obstructive Pulmonary Disease (COPD)
    - People who are morbidly obese (Body Mass Index (BMI) of 30 or greater)
- Also, last flu season, American Indians and Alaskan Natives seemed to be at higher risk of flu complications

Who else should get vaccinated?

Other people for whom vaccination is especially important are:

- People who live in nursing homes and other long-term care facilities
- People who live with or care for those at high risk for complications from flu, including:
    - Health care workers
    - Household contacts of persons at high risk for complications from the flu
    - Household contacts and caregivers of children younger than 5 years of age with particular emphasis on vaccinating contacts of children younger than 6 months of age (children younger than 6 months are at highest risk of flu-related complications but are too young to get vaccinated)

Use of the Nasal Spray Seasonal Flu Vaccine

Vaccination with the nasal-spray flu vaccine is an option for healthy* people 2-49 years of age who are not pregnant. Even people who live with or care for those in a high risk group (including health care workers) can get the nasal-spray flu vaccine as long as they are healthy themselves and are not pregnant. The one exception is health care workers who care for people with severely weakened immune systems who require a protected hospital environment; these people should get the inactivated flu vaccine (flu shot).

Who Should Not Be Vaccinated Against Seasonal Flu

Some people should not be vaccinated without first consulting a physician. They include:

- People who have a severe allergy to chicken eggs.
- People who have had a severe reaction to an influenza vaccination in the past.
- People who developed Guillian-Barré syndrome (GBS) within 6 weeks of getting an influenza vaccine previously.

- Children younger than 6 months of age (influenza vaccine is not approved for use in this age group).
- People who have a moderate or severe illness with a fever should wait to get vaccinated until their symptoms lessen.

If you have questions about whether you should get a flu vaccine, consult your health care provider.

For more about preventing the flu, see the following:

- Key Facts About Seasonal Flu Vaccine
- Influenza Antiviral Drugs
- Good Health Habits for Prevention
- The Flu: A Guide for Parents

CDC Says "Take 3" Actions To Fight The Flu

Flu is a serious contagious disease that can lead to hospitalization and even death. In 2009–2010, a new and very different flu virus (called *2009 H1N1*) spread worldwide causing the first flu pandemic in more than 40 years. Flu is unpredictable, but the Centers for Disease Control and Prevention (CDC) expects the 2009 H1N1 virus to spread this upcoming season along with other seasonal flu viruses.

CDC urges you to take the following actions to protect yourself and others from influenza (the flu):

Take time to get a flu vaccine.

- CDC recommends a yearly flu vaccine as the first and most important step in protecting against flu viruses.

- While there are many different flu viruses, the flu vaccine protects against the three viruses that research suggests will be most common.

- The 2010-2011 flu vaccine will protect against an influenza A H3N2 virus, an influenza B virus and the 2009 H1N1 virus that caused so much illness last season.

- Everyone 6 months of age and older should get vaccinated against the flu as soon as the 2010-2011 season vaccine is available.
- People at high risk of serious flu complications include young children, pregnant women, people with chronic health conditions like asthma, diabetes or heart and lung disease and people 65 years and older.
- Vaccination of high risk persons is especially important to decrease their risk of severe flu illness.
- Vaccination also is important for health care workers, and other people who live with or care for high risk people to keep from spreading flu to high risk people.
- Children younger than 6 months are at high risk of serious flu illness, but are too young to be vaccinated. People who care for them should be vaccinated instead.

Take everyday preventive actions to stop the spread of germs.

- Cover your nose and mouth with a tissue when you cough or sneeze. Throw the tissue in the trash after you use it.
- Wash your hands often with soap and water. If soap and water are not available, use an alcohol-based hand rub.*
- Avoid touching your eyes, nose and mouth. Germs spread this way.
- Try to avoid close contact with sick people.
- If you are sick with flu–like illness, CDC recommends that you stay home for at least 24 hours after your fever is gone except to get medical care or for other necessities. (Your fever should be gone without the use of a fever-reducing medicine.)
- While sick, limit contact with others as much as possible to keep from infecting them.

Take flu antiviral drugs if your doctor prescribes them.

- If you get the flu, antiviral drugs can treat your illness.
- Antiviral drugs are different from antibiotics. They are prescription medicines (pills, liquid or an inhaled powder) and are not available over-the-counter.
- Antiviral drugs can make illness milder and shorten the time you are sick. They may also prevent serious flu complications.
- It's very important that antiviral drugs be used early (within the first 2 days of symptoms) to treat people who are very sick (such as those who are hospitalized) or people who are sick with flu symptoms and who are at increased risk of severe flu illness, such as pregnant women, young children, people 65 and older and people with certain chronic health conditions.
- Flu-like symptoms include fever, cough, sore throat, runny or stuffy nose, body aches, headache, chills and fatigue. Some people may also have vomiting and diarrhea. People may be infected with the flu, and have respiratory symptoms without a fever.

Visit CDC's website to find out what to do if you get sick with the flu and how to care for someone at home who is sick with the flu. http://www.cdc.gov/flu/