Protocol TN08
Effects of Recombinant Human Glutamic Acid Decarboxylase (rhGAD65) Formulated in Alum (GAD-alum) on the Progression of Type 1 Diabetes in New Onset Subjects

Diane Wherrett, MD

Manual of Operations
Version 1.0 23Mar09

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 (01Dec08)

Title	Effects of Recombinant Human Glutamic Acid Decarboxylase (rhGAD65) Formulated in Alum (GAD-alum) 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	Diane Wherrett, MD
Accrual Objective	126 subjects over 2 years
Study Design	The study is a three-arm, multicenter, randomized, double-masked, placebo-controlled clinical trial. All groups will receive standard intensive diabetes treatment with insulin and dietary management.
Treatment Description	Recombinant human glutamic acid decarboxylase (rhGAD65), formulated in aluminum hydroxide is an antigen-specific immune modulator that has been shown to slow or prevent autoimmune destruction of pancreatic beta cells by inducing immune "tolerance". Participants will receive 3 injections consisting of 20µg of GAD-Alum x 3, 20µg of GAD-Alum x 2 plus one injection of placebo-Alum, or placebo-Alum x 3.
Study Duration	Total duration is approximately 4 years (2 years accrual and 2 years follow-up). Follow-up for up to 4 years may continue for those who have persistence of beta cell function after 2 years and/or detectable immunologic effects of treatment by

	descriptive analysis.
Objective	It is hypothesized that multiple injections with 20µg GAD-alum preserves endogenous insulin production in type 1-diabetes patients 3-45 years of age, when diagnosed within 3 months prior to the first injection.
Primary Outcome	The primary statistical hypothesis to be assessed in this study is whether the mean C-peptide value at one year for study subjects receiving three injections with GAD-Alum vaccine differs significantly from the mean value for placebo subjects, or if the mean C-peptide value for study subjects receiving two injections with GAD-Alum vaccine differs significantly from the mean value for placebo subjects.
Secondary Goals	The study will examine the effect of the proposed treatment on surrogate markers for immunologic effects, namely disease-specific outcomes and immunological outcomes.
Major Inclusion Criteria	Type 1 diabetes within past 3 months Age 3-45 years** Presence of GAD65 antibody

1.3 Participating Sites and Study Contacts

TN08 GAD 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 Site Trial Coordinator: Roberta Cook	Ph.: (352) 334-0857 Fax: (352) 392-4956 Email: schatda@peds.ufl.edu Ph.: (352) 334-0857 Fax: (352) 334-3865 Email: cookrb@peds.ufl.edu
Yale University School of Medicine New Haven, CT 06520-8089	02	Site PI: Kevan Herold, MD Site Trial Coordinator: Laurie Feldman	Ph.: (203) 785-6507 Fax: (203) 737-5637 Email: kevan.herold@yale.edu Ph.: (203) 737-2760 Fax: (203) 785-7450 Email: laurie.feldman@yale.edu
Children's Hospital of Los Angeles Los Angeles, CA 90081	04	Site PI: Francine Kaufman, MD Site Trial Coordinator: Mary Halvorson	Ph.: (323) 361-4606 Fax: (323) 953-1349 Email: fkaufman@chla.usc.edu Ph.: (323) 361 5963 Fax: (323) 953-1349 Email: mhalvorson@chla.usc.edu
Stanford University Stanford, CA 94305	05	Site PI: Darrell Wilson, MD Site Trial Coordinator: Trudy Esrey	Ph.: (650) 723-5791 Fax: (650) 725-8375 Email: Dwilson@stanford.edu Ph.: (650) 498-4450 Fax: (650) 725-5837 Email: tesrey@stanford.edu
University of Miami Miami, FL 33136	06	Site PI: Jennifer Marks, MD Site Trial Coordinator: Della Matheson	Ph.: (305) 243-6433 Fax: (305) 243-3313 Email: jmarks@miami.edu 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 Site Trial Coordinator: Susan George	Ph.: (303) 724-6714 Email: Peter.Gottlieb@ucdenver.edu Ph.: (303) 724-7501 Fax: (303) 724-7503 Email: susan.george@ucdenver.edu
Joslin Diabetes Center Boston, MA 02215	08	Site PI: Tihamer Orban, MD Site Trial Coordinator: Heyam Jalahej	Ph.: (617) 713-3442 Fax: (617) 732-2432 Email: torban@joslin.harvard.edu Ph.: (617) 732-2524 Fax: (617) 732-2432 Email: heyam.jalahej@joslin.harvard.edu
University of Minnesota Minneapolis, MN 55455	09	Site PI: Toni Moran, MD Site Trial Coordinator: Theresa Albright-Fisher	Ph: (612) 624-5409 Fax: (612) 626-5262 Email: moran001@umn.edu Ph.: (612) 626-2182 Fax: (612) 626-5206 Email: albr0088@umn.edu
Benaroya Research Institute Seattle, WA 982101	10	Site PI: Carla Greenbaum, MD Site Trial Coordinator: Marli McCulloch-Olson	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 Ph.: (206) 515-5233 Fax: (206) 515-5239 Email: Marli@benaroyaresearch.org
University of California – San Francisco San Francisco, CA 94143	11	Site PI: Stephen Gitelman, MD Site Trial Coordinator: Celia Hamilton	Ph.: (415) 476-3748 Fax: (415) 476-8214 Email: sgitelma@peds.ucsf.edu 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 Site Trial Coordinator: Marilyn Alford	Ph.: (214) 648-2017 Fax: (214) 648-4854 Email: philip.raskin@utsouthwestern.edu Ph.: (214) 648-4844 Fax: (214) 648-3816 Email: Marilyn.Alford@UTSouthwestern.edu
The Hospital for Sick Children Toronto, ON Canada, MSG-1X8	13	Site PI: Diane Wherrett, MD Site Trial Coordinator: TBA	Ph.: (416) 813-8159 Fax: (416) 813-6304 Email: diane.wherrett@sickkids.ca Ph.: Fax: Email:
University of Pittsburgh Pittsburgh, PA 15201	14	Site PI: Dorothy Becker, MD Site Trial Coordinator: Karen Riley	Ph.: (412) 692-5179 Fax: (412) 692-5834 Email: dorothy.becker@chp.edu 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 Site Trial Coordinator: Ellen Greenberg	Ph: (212) 851-5492 Fax: (212) 851-5460 Email: rsg2@columbia.edu 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 Site Trial Coordinator: Martha Mendez	Ph.: (317) 274-1010 Fax: (317) 278-0264 Email: mpescov@iupui.edu Ph.: (317) 278-8879 Fax: (317) 274-2579 Email: mwmendez@iupui.edu

TN08 GAD Study TrialNet Coordinating Center (TNCC)		
USF TrialNet Coordinating Center (TNCC) University of South Florida Pediatrics Epidemiology Center Tampa, FL 33615	Primary Contact: Joy Ramiro	Ph.: (813) 396-9211 Fax: 813-910-5994 Email: joy.ramiro@epi.usf.edu
	Secondary Contact: AQesha Ritzie	Ph.: (813) 396-2681 Fax: 813-910-5994 Email: aqesha.ritzie@epi.usf.edu

TN08 GAD Study CENTRAL PHARMACY		
EMINENT Services Corporation 7495 New Technology Way Frederick, MD 21703-9401	Raghu Yaramolu	Ph.: (240) 629-1972 Ext 107 Fax: (240) 629-3298 Email: ryaramolu@emiserv.com

TN08 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 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
Islet Autoantibodies BAA	Attn: BAA Lab Barbara Davis Center 1775 Aurora Court, UC Denver, AMC M20-4201E Aurora, CO 80045	Liping Yu	Ph.: (303) 724-6808 Email: Liping.Yu@ucdenver.edu
Viral Serology: CMV IgG; EBV IgG and IgM	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
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

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.

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 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 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 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 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 each person listed.
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

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 annually. The duality of interest forms can either be completed in hard copy and faxed to the TNCC (813 910 5994) or it can be completed online. A PDF 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.

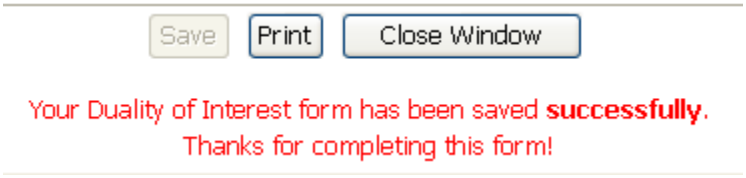
To access the online form:

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

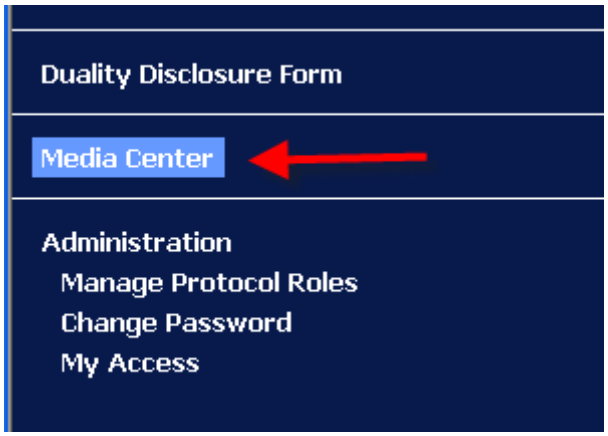
3.4 Study/System Training

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

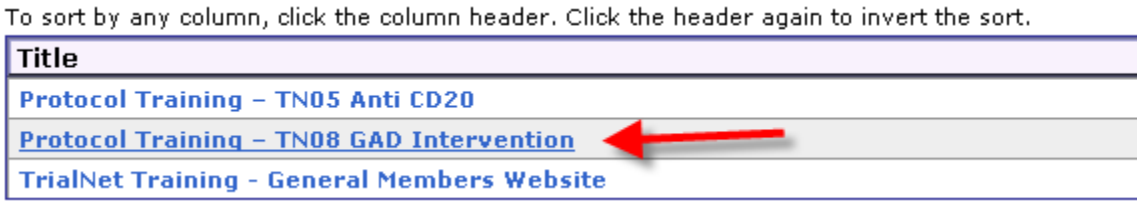
Demonstration and training videos are available online. **You must have windows media player** in order see the videos; they can be viewed at any time by navigating to the online media center as follows:

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



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

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) TN08 Protocol Overview: Provides a description of the protocol, eligibility criteria, purpose, specific aims, and details of procedures
2) Neurologic Assessment: Provides a visual tutorial on how to conduct a specific neurologic assessment
3) TN08 Pharmacy Training: Provides an overview of pharmacy related procedures including drug ordering, dispensing, agent return, etc
4) TN08 Online Protocol Tools: Provides a description of tools available on the TNCC Protocol Manager page including protocol documents, checklists, reports, source documents, MOO, pharmacy manual, etc
5) TN08 Online Forms By Visit: Provides a brief overview of e-CRF’s available for the study by visit
6) TN08 Online Participant Registration: Provides a guided tutorial of how to register a participant
7) TN08 Online Treatment Assignment and Randomization: Provides a guided tutorial of how to assign treatment to a participant
8) TN08 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 GAD Certification Quiz

The GAD 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

126 subjects over 2 years
Activation date: February 27, 2009

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.
- 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:
- Be 3 to 45 years of age at the time of randomization, this indicates that at the time of randomization the participant has passed his/her 3rd birthday, but has not passed his/her 46th birthday

- 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

- 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
- Presence of GAD65 antibodies
- At least one month from last immunization
- Be willing to comply with intensive diabetes management
- If female with reproductive potential, be willing to avoid pregnancy and have a negative pregnancy test. A urine pregnancy test will be conducted at Screening, Baseline, Days 28 and 84, months 6, 12, 18 and 24. Acceptable forms of birth control include, but are not limited to:
    - Abstinence
    - Barrier methods (condom, diaphragm, cervical cap, sponge, or spermicide)
    - Contraceptives (oral or implant)
    - Surgical methods (sterilization or intrauterine devices)
- 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.
- Be willing to forgo routine clinical immunizations during the first 100 days after initial injection of GAD-Alum/Alum.

Exclusion Criteria:

The participant MUST NOT:

- 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.
- On-going use of medications known to influence glucose tolerance.
- 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.

- Have history of malignancies
- Be currently using non-insulin pharmaceuticals to affect glycemic control. If a participant is willing to stop therapy with these agents then they will be eligible for study participation following a two week (14 day) washout period.
- Have any acute or chronic complicating medical issues or abnormal clinical laboratory results that interfere with study conduct or cause increased risk including neurological abnormalities.
- Have a history of epilepsy, significant head trauma or cerebrovascular accident or clinical features of continuous motor unit activity in proximal muscles.
- In ability or unwillingness to comply with the provisions of this protocol
- Have an active infection or 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.
- Have serologic evidence of current or past HIV, Hepatitis B, 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.

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 H 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

Visit	-1	0	1	2	3	4	5	6	7	8	9	10	11[4]+
~Month of Trial	-X	0		1		3		6	9	12	18	24	30[4]+
~Day of Trial	-X	0	14	28[1]	35[1]	84[1]	91[1]						
Procedures/Assessments													
Consent Form(s)	X	X											
Volunteer Understanding Quiz	X	X*											
Conmeds	X	X		X		X		X		X	X	X	X
Medical History	X		X		X	X	X	X	X	X	X	X	X
Physical Exam	X	X		X		X		X		X	X	X	X
Specific Neurological Assess.	X	X		X		X		X		X	X	X	X
PPD Test	X												
Urine Pregnancy Test	X	X		X		X		X		X	X	X	X
AE assessment		X	X	X	X	X	X	X	X	X	X	X	X
Randomization/Treatment Assign		X											
Study Agent Administration		X		X		X							
Remind Subj. Bring Glu/Ins Records	X		X		X		X	X	X	X	X		
Collect Diabetes Management Info.		X		X		X		X	X	X	X	X	X
Blood Draws													
MMTT 4 hr >12 years old	X											X	
MMTT 2 hr >12 years old						X		X	X	X	X		X
MMTT 2 hr =/<12 years old	X					X		X	X	X	X	X	X
CBC	X						X					X	
Chemistries	X					X						X	
HIV/HepB/HepC	X												
Autoantibodies	X					X		X		X	X	X	X
HLA Determination	X												
EVB/CMV Viral Serology	X												
HbA1c		X				X		X	X	X	X	X	X
Cellular Immunoblot		X					X						
ITN Whole Blood- PBMC/Plasma[2]	X	X	X	X	X	X	X	X		X		X	
ITN Whole Blood- RNA[2]		X		X	X	X	X	X		X		X	
Mechanistic Serum[2]		X	X	X	X		X			X		X	
e-CRFs													
Screening ICF Verification	X												
Family History	X												
Demographics	X												
Screening Medical History	X												
Eligibility form		X											
Randomization		X											
Physical Exam	X	X		X		X		X		X	X	X	X
Concomitant Medications	X	X[3]		X[3]		X[3]		X[3]		X[3]	X[3]	X[3]	X[3]

Specimen Collection Form(s)	X	X	X	X	X	X	X	X	X	X	X	X	X
Interim Medical History		X		X		X		X		X	X	X	X
Diabetes Management		X		X		X		X	X	X	X	X	X
Study Drug Administration		X		X		X							
AE Form		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Visit Windows													
Visit Window	NA	X[5]	+/- 3 days	-2 / +7 days	+/- 3 days	-2 / +7 days	+ 3 days	+/- 2 weeks					

[1]The target date for the 2nd and 3rd study drug administration will be set in accordance with the previous dose so that the first and second doses will be 4 weeks apart and the third dose will be 8 weeks later. Similarly, the visit target dates after the 2nd and 3rd study drug administration will be scheduled in relation to the actual date the injection was done.

[2] With permission of subject

[3] Complete form only if changes (conmed form) / if applicable (AE form- reportable adverse event)

[4] 30month+ visits will continue until last subject has met 24month visit

[5] Within 37 days of screening MMTT and 100 days from diagnosis

5.2 Visit -1 Screening:

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 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 TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

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 to ensure the subject understands the study and their responsibilities. The volunteer survey is located online in the TN08 Protocol Area, folder entitled "TN08 – Protocol Documents"

Step 4. Clinical Assessments- use source documents to collect information for each of the clinical assessments. The source documents are located online in the TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

a. Collect subject's medical history
b. Ask the subject about what medications he/she is currently taking
c. Conduct a physical exam
d. Conduct the Specific Neurological Assessment

Step 5. Tests and Assays- follow instructions in section 6.4 of this document for collection of specimens

a. Conduct a PPD
b. Conduct a Urine Pregnancy Test if participant is female of childbearing potential
c. Conduct a 4-hour MMTT (or 2-hour MMTT if ≤ 12 years old)
d. Collect blood for:
    i. CBC with differential
    ii. Chemistries
    iii. HIV/Hep B/Hep C
    iv. Autoantibodies
    v. HLA Determination
    vi. EBV/CMV Viral Serology
    vii. Mechanistic Assessments- ITN Whole blood – PBMC/Plasma

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

Step 7. Register the participant in the online system

Step 8. Enter data collected on source documents into the e-CRF's online. Please note, you must enter the Demographics e-CRF in order for the correct MMTT collection time points to display on the specimen collection form.

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

5.3 Visit 0 Baseline:

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

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

Step 4. If study drug is needed,
   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 Fisher 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 TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

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 TN08 Protocol Area, folder entitled "TN08 – Protocol Documents"

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 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 source documents are located online in the TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"
   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
d. Conduct the Specific Neurological Assessment
e. Obtain information about Diabetes Management
f. Ask the participant if they have experienced any adverse events

Step 6. Protocol-Specific Activities: administer **first** dose of study agent. Use source documents to collect information for the administration of study drug. The source documents are located online in the TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

Step 7. 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. HbA1c
      ii. Mechanistic Assessments- ITN Whole blood – PBMC/Plasma
      iii. Mechanistic Assessments- ITN Whole blood – RNA
      iv. Mechanistic Assessments- Cellular Immunoblot
      v. Mechanistic Assessments- Mechanistic Serum

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

5.4 Visit 1 (Day 14):

Window: +/- 3 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 TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

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 source documents are located online in the TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

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. 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. Mechanistic Assessments- ITN Whole blood – PBMC/Plasma
    ii. Mechanistic Assessments- Mechanistic Serum

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

Step 5. Enter data collected (as applicable) 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.

Step 8. Retain all materials from visit and source documents in an organized fashion in a secured, double-locked room.

5.5 Visit 2 (Day 28):

Window: -2 / +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 TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

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 source documents are located online in the TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

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
d. Conduct the Specific Neurological Assessment
e. Obtain information about Diabetes Management
f. Ask the participant if they have experienced any adverse events

Step 3. Protocol-Specific Activities: administer **second** dose of study agent. Use source documents to collect information for the administration of study drug. The source documents are located online in the TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

Step 4. 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. Mechanistic Assessments- ITN Whole blood – PBMC/Plasma
    ii. Mechanistic Assessments- ITN Whole blood – RNA
    iii. Mechanistic Assessments- Mechanistic Serum

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 of this document for packaging and shipment of specimens.

Step 8. Retain all materials from visit and source documents in an organized fashion in a secured, double-locked room.

5.6 Visit 3 (Day 35):

Window: +/- 3 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 TN08 Protocol Area, folder entitled “TN08 – Forms: Source Documents and Visit Checklists”

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 source documents are located online in the TN08 Protocol Area, folder entitled “TN08 – Forms: Source Documents and Visit Checklists”

a. Collect subject’s medical history (any changes since last visit)
b. Ask if the subject about his/her concomitant medications (changes since last visit)
c. 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. Mechanistic Assessments- ITN Whole blood – PBMC/Plasma
   ii. Mechanistic Assessments- ITN Whole blood – RNA
   iii. Mechanistic Assessments- Mechanistic Serum

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

Step 5. Enter data collected (as applicable) 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 of this document for packaging and shipment of specimens.

Step 8. Retain all materials from visit and source documents in an organized fashion in a secured, double-locked room.

5.7 Visit 4 (Day 84):

Window: -2 / +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. 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 TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

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 source documents are located online in the TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

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
d. Conduct the Specific Neurological Assessment
e. Obtain information about Diabetes Management
f. Ask the participant if they have experienced any adverse events

Step 3. Protocol-Specific Activities: administer **third** dose of study agent. Use source documents to collect information for the administration of study drug. The source documents are located online in the TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

Step 4. 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. Chemistries
    ii. Autoantibodies
    iii. HbA1c
    iv. Mechanistic Assessments- ITN Whole blood – PBMC/Plasma
    v. Mechanistic Assessments- ITN Whole blood – RNA

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.

Step 8. Retain all materials from visit and source documents in an organized fashion in a secured, double-locked room.

5.8 Visit 5 (Day 91):

Window: +3 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 TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

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 source documents are located online in the TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

a. Collect subject's medical history (any changes since last visit)
b. Ask if the subject about his/her concomitant medications (changes since last visit)
c. 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. CBC with differential
    ii. Mechanistic Assessments- Cellular Immunoblot
    iii. Mechanistic Assessments- ITN Whole blood – PBMC/Plasma
    iv. Mechanistic Assessments- ITN Whole blood – RNA
    v. Mechanistic Assessments- Mechanistic Serum

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

Step 5. Enter data collected (as applicable) 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.

Step 8. Retain all materials from visit and source documents in an organized fashion in a secured, double-locked room.

5.9 Visit 6 (Month 6):

Window: +/- 2 weeks

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 TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

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 source documents are located online in the TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

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
d. Conduct the Specific Neurological Assessment
e. Obtain information about Diabetes Management
f. 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. Autoantibodies
    ii. HbA1c
    iii. Mechanistic Assessments- ITN Whole blood – PBMC/Plasma
    iv. Mechanistic Assessments- ITN 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.

Step 8. Retain all materials from visit and source documents in an organized fashion in a secured, double-locked room.

5.10 Visit 7 (Month 9):

Window: +/- 2 weeks

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 TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

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 source documents are located online in the TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

a. Collect subject's medical history (any changes since last visit)
b. Obtain information about Diabetes Management
c. 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
b. Collect blood for:
    i. HbA1c

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.

Step 8. Retain all materials from visit and source documents in an organized fashion in a secured, double-locked room.

5.11 Visit 8 (Month 12):

Window: +/- 2 weeks

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 TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

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 source documents are located online in the TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

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
d. Conduct the Specific Neurological Assessment
e. Obtain information about Diabetes Management
f. 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. Autoantibodies
    ii. HbA1c
    iii. Mechanistic Assessments- ITN Whole blood – PBMC/Plasma
    iv. Mechanistic Assessments- ITN Whole blood – RNA
    v. Mechanistic Assessments- Mechanistic Serum

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.

Step 8. Retain all materials from visit and source documents in an organized fashion in a secured, double-locked room.

5.12 Visit 9 (Month 18):

Window: +/- 2 weeks

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 TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

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 source documents are located online in the TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

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
d. Conduct the Specific Neurological Assessment
e. Obtain information about Diabetes Management
f. 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. Autoantibodies
    ii. HbA1c

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.

Step 8. Retain all materials from visit and source documents in an organized fashion in a secured, double-locked room.

5.13 Visit 10 (Month 24):

Window: +/- 2 weeks

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 TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

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 source documents are located online in the TN08 Protocol Area, folder entitled "TN08 – Forms: Source Documents and Visit Checklists"

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
d. Conduct the Specific Neurological Assessment
e. Obtain information about Diabetes Management
f. 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
a. Conduct a 4-hour MMTT (or 2-hour MMTT if ≤ 12 years old)
b. Collect blood for:
    i. CBC with differential
    ii. Chemistries
    iii. Autoantibodies
    iv. HbA1c
    v. Mechanistic Assessments- ITN Whole blood – PBMC/Plasma
    vi. Mechanistic Assessments- ITN Whole blood – RNA
    vii. Mechanistic Assessments- Mechanistic Serum

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

5.14 End of Study Participation

5.14.1 Participant Registered in Error

If it is determined that a site has registered a participant in error it is important to contact the TNCC. The TNCC will remove the erroneous entry from the online data capture system.

5.14.2 Participant Withdrawal or Lost to Follow-up

If it is determined that a participant has withdrawn or has been lost to follow up, the site should complete the "Change of Status" e-CRF in the online electronic data capture system and indicate that the subject has withdrawn/lost to follow up.

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

5.14.3 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. 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. DESCRIPTION OF AND INSTRUCTIONS FOR STUDY PROCEDURES

6.1 Quizzes

6.1.1 Volunteer Survey (Visit -1 OR Visit 0)

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.

6.2 Protocol-Specific Activities

6.2.1 Randomization/Treatment Assignment (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 three groups:

- 42 participants will be assigned to receive 3 injections with 20µg GAD-Alum; or
- 42 participants will be assigned to receive 2 injections with 20µg GAD-Alum followed by one injection with Alum alone; or
- 42 participants will be assigned to receive 3 injections of Alum only

Participants will be randomized, in approximately equal numbers. 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:

a. Subject has signed the Screening and Intervention Consent (Screening and Intervention Assent if applicable),

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

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

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.

6.2.2 Study Drug Administration (Visits 0, 2, 4)

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 3 subcutaneous injections of 0.8mLof GAD-Alum OR 0.8mL of GAD-Alum x2 plus 1x injection of placebo-Alum OR placebo-Alum x 3. The first injection is given at baseline (day 0), the second injection is given 4 weeks later, and the third injection is given at 8 weeks after the second. Dosing will not be done in subjects with a febrile illness within the previous 24 hours. These subjects will be rescheduled for another day within a five day window.

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, kit # used, vial # dispensed on to the Pharmacy Agent Accountability Log
e. Dispense to the site coordinator from the corresponding kit the appropriate vial and syringe for the appropriate visit/subcutaneous infusion.

Step 3. Prepare the syringe: k. The individual preparing and 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 syringe. The syringe should be prepared immediately prior to study agent administration.
a. Use gloves
b. Gently invert the vial several times
c. Do not allow vial contents to settle
d. Pre-fill the syringe with slightly more that 0.5mL of the study agent
e. Prep the syringe and needle, removing any air bubbles, and ensuring that the remaining amount in the syringe is precisely 0.5mL of study agent
f. Do not allow the study agent to settle in the syringe.

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 during 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).

Step 5. Complete online e-CRF's
a. FOR BASELINE ONLY: complete Treatment Start Date" form
b. FOR ALL STDUY DRUG ADMINISTRATION VISITS: Complete e-CRF: Study Drug Administration form

6.2.3 AE (Adverse Event) Assessment (All visits except Visit -1)

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 TN08, only AE's determined to be CTC AE3.0 grade 2 or greater are reportable.

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

Procedure:
Step 1. Utilize source document as 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

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, the coordinator should complete FORM FDA3500A, submit to the FDA, and immediately fax to the TNCC.

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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 (Visits 0-2, 4, 6, 8- 10+)

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

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 Physical Exam (Visit -1, 0, 2, 4, 6, 8- 10+)

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 Specific Neurological Assessment (Visit -1, 0, 2, 4, 6, 8-10+)

Definition: The patients will undergo a standardized clinical neurological examination. The neurological tests are performed in order to detect possible mild signs of neuromuscular disease such as disturbance of strength, balance and coordination. The neurological examination includes:

Extremity reflexes
Romberg (balance and coordination)
Walk on a line, 2 meters (balance and coordination)
Standing on one leg, left and right, 15 seconds per leg (balance and coordination)
Finger-finger (coordination)
Finger-nose (coordination)
Mimic (cranial nerves)
Babinski reflex (central function)
Muscle strength (shake hands) biceps, triceps, distal extensors and flexors.

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 Concomitant Medications (Visit -1, 0, 2, 4, 6, 8-10+)

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.

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)

6.4 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).

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 (Visit -1, 0, 2, 4, 6, 8-10+)

Definition: The urine pregnancy test is 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, 4, 6- 10+)

Definitions: MMTT is commonly used in the U.S. It is a liquid meal (Sustacal/Boost) 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 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 ?. 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 TN08 study:
a. 4-hour MMTT (Visits -1 and Visit 10)
Note: During visit -1 and visit 10, if the participant is ≤ 12 years of age, then a 2-hour MMTT will be done.
b. 2-hour MMTT (Visit 4, Visit 6, Visits 7-9)

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

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

12-Hour Clock	24-Hour Clock
1:00 pm	13:00

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

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 to be given to the participant::

DOSE CALCULATION WORKSHEET

BOOST Dose:

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

BOOST Dose Given:

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

BOOST cans contain 8 fluid-ounces (240 mL)

BOOST Dose Calculation

Subject's weight in pounds_____ multiply by 0.454 = _____kg
Subject's weight in kg _____ multiply by 6 = _____ mL of BOOST (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 49.9 kg x 6 = 299.4 mL (about one and one-fourth cans)

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 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®, 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 - this is the "0 minute" sample
c. Meal consumption - Start the clock at the beginning of the drink. The dose of Boost 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 Taken 1.2 mL gray top tube	C-peptide Sample Taken 1.2 mL lavender top EDTA tube
-10	X	X
0	X	X
Drink Boost		
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.

Supplies Needed for Collection for MMTT

Supply	Collection/Shipment
4-hr MMTT: 11 x 1.2 mL lavender top EDTA collection tubes (C-	Collection

Peptide)	
4-hr MMTT: 11 x 1.2 mL gray top Oxalate/Fluoride collection tubes (Glucose)	Collection
4-hr MMTT: 11 x 1.8 mL lavender top etched cryovial (C-Peptide)	Shipment
4-hr MMTT: 11 x 1.8 mL gray top etched cryovial (Glucose)	Shipment
2-hr MMTT: 7 x 1.2 mL lavender top EDTA collection tubes (C-Peptide)	Collection
2-hr MMTT: 7 x 1.2 mL gray top Oxalate/Fluoride collection tubes (Glucose)	Collection
2-hr MMTT: 7 x 1.8 mL lavender top etched cryovial (C-Peptide)	Shipment
2-hr MMTT: 7 x 1.8 mL gray top etched cryovial (Glucose)	Shipment
Alcohol- Proof Pen	Collection
2" Partitioned freezer storage box	Shipment
Biohazard Ziploc bag with an absorbent sheet	Shipment
Large Styrofoam Box	Shipment
Dry Ice (at least 5lbs or 3 kg)	Shipment
Tape	Shipment
Labels: (1) Black Diamond UN1845 Dry Ice Label (2) Diamond UN 3373 Biological Specimen Category B	Shipment
Pre-paid FedEx airbill	Shipment

Procedure

Step 1. Collect Specimen MMTT (4-hour or 2-hour)

a. Label 11 (or seven) 1.2 mL gray top collection tube with the specimen type (Glucose) and label eleven (or seven) 1.2 lavender top collection tube with the specimen (C-peptide).
b. Scan each (eleven or seven) 1.8 mL gray top etched cryovial and each (eleven or seven) 1.8 mL lavender top etched cryovial into the SCF. Write the first three letters of the participant's name, the date of draw (MM/DD/YYYY), and specific time points with an alcohol-proof pen on the tube or on a separate label; apply the label vertically
c. Draw 11 (or seven) 1.2 mL of blood (glucose) into each gray top collection tubes and eleven (or seven) 1.2 mL of blood (C-peptide) into each lavender top collection tubes at the specified time-points.
d. Immediately invert each tube gently 8 -10 times to mix sample, avoid jarring or shaking, then place upright on ice or in refrigerator.
e. Centrifuge each sample for 10 minutes in a chilled centrifuge within 1 hour after drawing.
f. Transfer plasma into the appropriate 1.8 mL cryovials. Screw tops on tightly to avoid leakage.
g. Place specimens upright in a 2" partitioned freezer storage box. Freeze samples at -20° C.

Step 2. Complete e-CRF specimen collection form

Step 3. Use shipment system to ship specimens

Step 4. Ship Specimens

a. Place the 2" partitioned freezer storage box into a biohazard Ziploc bag with an absorbent sheet.
b. Place a printed copy of the shipment manifest in the outside sleeve of the bag.

c. Place the bag into a larger Styrofoam box filled to capacity with dry ice (at least 5 lbs or 3 kg) and tape outer cardboard box securely closed.
d. Affix the following two labels to the outside of the box:
   (1) Black Diamond UN1845 Dry Ice Label,
   (2) Diamond UN 3373 Biological Specimen Category B
e. Prepare and print a pre-paid airbill to FedEx all samples Priority Overnight to:
   Specimen Processing,
   Northwest Lipid Research Laboratories
   401 Queen Anne Avenue North
   Seattle, WA 98109-4517
   Phone: (206) 685-3327

Note: Ship specimens Monday – Thursday only (except days before U.S. federal holidays)

6.4.4 CBC (Complete Blood Count) with Differential (Visit -1, 5, 10)

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 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

6.4.5 Chemistries (Visit -1, 4,10)

Definition: Chemistry screening is a blood test that measures the level of a number of chemical substances or part of the blood. For this study the chemistries that will be assessed are sodium, potassium, chloride, CO2, glucose, BUN, and creatinine.

Supplies Needed:

Supply	Collection/Shipment
1 x 4 mL plain red top tube	Collection
Alcohol Proof Pen	Collection
1 x 2 mL etched amber cryovial	Shipment
Styrofoam Tube Holder	Shipment
Cardboard Sleeve	Shipment
Biohazard Ziploc Bag	Shipment
Cold Packs	Shipment
Tape	Shipment
Label: Diamond UN 3373 Biological Specimen Category B	Shipment

Pre-paid FedEx airbill	Shipment

Procedure:

Step 1. Collect Specimen

a. Label one 4 mL plain red top tube with the specimen type (CHEMISTRIES).
b. Scan the 2mL etched amber cryovial into the SCF. Write the first three letters of the participant's name and the date of draw (MM/DD/YYYY) with an alcohol-proof pen on the tube or on a separate label; apply the label vertically
c. Draw 4 mL of blood into 4 mL plain red top tube.
d. Invert the tube gently 5 times and place upright in a tube rack.
e. Allow blood to clot for 60 minutes at room temperature (65-75°F)
f. Centrifuge tube for 10 minutes
g. Transfer serum into 2 mL amber cryovial. Screw the top on tightly to prevent leakage
h. Keep the amber cryovial on ice or in a refrigerator (4°C) until ready for shipping.

Step 2. Complete e-CRF specimen collection form

Step 3. Use shipment system to ship specimens

Step 4. Ship Specimens

a. Place the amber cryovial into a Styrofoam tube holder with an absorbent pad.
b. Place the Styrofoam tube holder into a cardboard sleeve and then into a biohazard Ziploc bag. Place shipment manifest in the outside sleeve of the bag.
c. Ship sample with cold packs in a Styrofoam shipping container.
d. Affix return address label on the inside flap of box since core lab will return shipping boxes by FedEx.
e. Tape outer box securely closed.
f. Affix the following label to the outside of the box: Diamond UN 3373 Biological Specimen Category B
g. Prepare and print a pre-paid FedEx airbill and ship Priority Overnight to:

Specimen Processing
Northwest Lipid Research Laboratories
401 Queen Anne Avenue North
Seattle, WA 98109-4517
Phone: (206) 685-3327

Ship specimens Monday – Thursday only (except days before U.S. federal holidays)

6.4.6 HIV/HepB/HepC and EVB/CMV Viral Serology (Visit -1):

Definition: Viral Serology: This unit provides serologic testing for viral diseases. For the TN08 study the following are viral serologies that will be assessed:
Antibodies to HIV, hepatitis B (antiHBcAb, HbsAg,), hepatitis C (HCV),Cytomegalovirus (CMV IgG)) Epstein-Barr Virus (EBV IgG and IgM).

Supplies Needed for HIV/ HEPB/HEPC:

Supply	Collection/Shipment
1 x 4 mL plain red top tube	Collection
Alcohol-proof pen	Collection
1 x 4 mL etched cryovial	Shipment
3" partitioned freezer storage box	Shipment
Biohazard Ziploc bag with absorbent sheet	Shipment

Large Styrofoam box	Shipment
Dry Ice 5lbs or 3 kg	Shipment
Tape	Shipment
Two Labels: • Black Diamond UN1845 Dry Ice Label • Diamond UN3373 Diagnostic Specimen Label	Shipment
Pre-printed Fed Ex label	Shipment

Procedure:

Step 1. Collection of HIV/HEP B/HEP C

a. Label one 4 mL plain red top tube with the specimen type (HIV/HEPB/HEPC).
b. Scan the 4mL etched cryovial into the SCF. Write the first three letters of the participant's name and the date of draw (MM/DD/YYYY) with an alcohol-proof pen on the tube or on a separate label; apply the label vertically.
c. Draw 4 mL blood into the red top collection top tube.
d. Rotate tube gently and place upright in tube rack.
e. Allow blood to clot for 60 minutes at room temperature (65°-75°F).
f. Centrifuge sample for 10 minutes.
g. Transfer serum into 4 mL etched cryovial. Screw the top on tightly to prevent leakage.
h. Place sample upright in a 3" partitioned freezer storage box.
i. Freeze at -20°C

Step 2. Complete e-CRF specimen collection form

Step 3. Use shipment system to ship specimens

Step 4. Shipment of HIV/HEP B/HEP C

a. Place the 3" partitioned freezer storage box into a biohazard Ziploc bag with an absorbent sheet.
b. Place shipment manifest in the outside sleeve of the bag.
c. Place the bag into a large Styrofoam box filled to capacity with dry ice (at least 5 lbs or 3 kg) and tape outer cardboard box securely closed.
d. Affix the following two labels to the outside of the box:
    1) Black Diamond UN1845 Dry Ice Label
    2) Diamond UN 3373 Diagnostic Specimen Label (Placed on the same side as the Black Diamond Dry Ice Label)
e. Prepare and print a pre-paid airbill to FedEx all samples Priority Overnight to:
    Specimen Processing,
    Northwest Lipid Research Laboratories
    401 Queen Anne Avenue North
    Seattle, WA 98109-4517
    Phone: (206) 685-3327

Ship specimens Monday – Thursday only (except days before U.S. federal holidays).

Supplies Needed for EBV/CMV Viral Serology:

Supply	Collection/Shipment
1 x 3 mL red top collection tube	Collection
Alcohol-proof pen	Collection

1 x 1.8 mL red top etched cryovial	Shipment
3" partitioned freezer storage box	Shipment
Biohazard Ziploc bag with absorbent sheet	Shipment
Large Styrofoam box	Shipment
Dry Ice 5lbs or 3 kg	Shipment
Tape	Shipment
Two Labels: • Black Diamond UN1845 Dry Ice Label • Diamond UN 3373 Biological Specimen Category B	Shipment
Pre-printed Fed Ex label	Shipment

Procedure:

Step 1. Collection of EBV/CMV

a. Label one 3 mL red top collection with the specimen type (EBV/CMV).
b. Scan the 1.8mL etched cryovial into the SCF. Write the first three letters of the participant's name and the date of draw (MM/DD/YYYY) with an alcohol-proof pen on the tube or on a separate label; apply the label vertically
c. Draw 2 mL of blood into the 3 mL red top tube.
d. Rotate tube gently and place upright in tube rack.
e. Allow blood to clot for 60 minutes at room temperature (65-75° F).
f. Centrifuge sample for 10 minutes.
g. Transfer serum into 1.8 mL etched cryovial. Screw the top on tightly to prevent leakage.
h. Place sample upright in a 3" partitioned freezer storage box.
i. Freeze at -20° C

Step 2. Complete e-CRF specimen collection form

Step 3. Use shipment system to ship specimens

Step 4. Shipment of EBV/CMV

a. Place the 3" partitioned freezer storage box into a biohazard Ziploc bag with an absorbent sheet.
b. Place the shipment manifest into the outside sleeve of the bag.
c. Place the bag into a large Styrofoam box filled to capacity with dry ice (at least 5 lbs or 3 kg) and tape outer cardboard box securely closed.
d. Affix the following two labels to the outside of the box:
    1) Black Diamond UN1845 Dry Ice Label
    2) Diamond UN 3373 Biological Specimen Category B
e. Prepare and print a pre-paid airbill to FedEx all samples Priority Overnight to:

Viral Clinical Lab
University of Colorado Hospital
12401 E 17th Ave
Clinical Lab - LOB Room 253
Aurora, CO 80045
Phone: (720) 848-4401

Ship specimens Monday – Thursday only (except days before U.S. federal holidays)

6.4.7 Autoantibodies (Visit -1, 4, 6, 8-10)

Definition: Autoantibodies are antibodies (a type of protein) manufactured by the immune system that are directed against one or more of the individual's own proteins.

Supplies Needed:

Supply	Collection/Shipment
1 x 2.6 mL SST Gel Tube with Clotting Activator, Sarstedt	Collection
Alcohol proof pen	Collection
1 x 1.8 mL red top etched cryovial	Shipment
3" partitioned freezer storage box	Shipment
Biohazard Ziploc bag with an absorbent sheet	Shipment
Large Styrofoam shipping container	Shipment
Dry ice (at least 5 lbs. or 3 kg	Shipment
Tape (to seal box)	Shipment
Black Diamond UN1845 Dry Ice Label	Shipment
Diamond UN 3373 Biological Specimen Category B Label (placed on the same side as the Black Diamond Dry Ice Label).	Shipment
Pre-paid FedEx airbill	Shipment

Procedure:

Step 1. Collect Specimen

a. Label one 2.6 mL SST Gel Tube with clotting activator, Sarstedt, with the specimen type (AA).
b. Scan one red topped 1.8 mL red top etched cryovial into the SCF. Write the first three letters of the participant's name and the date of draw (MM/DD/YYYY) with an alcohol-proof pen on the tube or on a separate label; apply the label vertically
c. Draw 2 mL of blood into the 2.6 mL SST Gel Tube with clotting activator, Sarstedt.
d. Gently invert tube 5 times and place upright in a tube rack. Allow blood to clot for 20-30 minutes at room temperature (65-75º F).
e. Centrifuge at full speed for 15 minutes. Transfer serum into the 1.8 mL red top etched cryovial. Screw top on tightly to prevent leakage.
f. Place samples upright in a 3" partitioned freezer storage box. Freeze at -20º C.
g. If shipping unfrozen same day, skip step 4 and refer to step 5.

Step 2. Complete e-CRF specimen collection form

Step 3. Use shipment system to ship specimens

Step 4. Shipment of autoantibodies specimens **frozen**

a. Ship batched frozen samples weekly.
b. Place the 3" partitioned freezer storage box with samples into a biohazard Ziploc bag with an absorbent sheet.
c. Place a printed copy of the shipment manifest in the outside sleeve of the bag.
d. Place the bag into a large Styrofoam shipping container filled to capacity with dry ice (at least 5 lbs. or 3 kg) and tape outer cardboard box securely closed.
e. Affix the following labels to the outside of the box:
    i. Black Diamond UN1845 Dry Ice Label
    ii. Diamond UN 3373 Biological Specimen Category B Label (placed on the same side as the Black Diamond Dry Ice Label).
f. Prepare and print a pre-paid FedEx airbill to ship specimen Priority Overnight to:

TrialNet Core Screening Laboratory (UFDRL)
University of Florida
4800 SW 35th Drive
Gainesville Florida, 32608
Phone: (352) 265-9900

Ship specimens Monday – Thursday only (except days before a United States federal holiday)

Step 5. Shipment of autoantibodies specimens **unfrozen (the SAME DAY)**:

a. Place tubes into a Styrofoam tube holder with an absorbent pad.
b. Place the tube holder into cardboard sleeve and into a biohazard Ziploc bag
c. Place the shipment manifest into the outside pocket of the bag.
d. Place the bag into a FedEx Diagnostic Specimen Envelope and ship to:

TrialNet Core Screening Laboratory (UFDRL)
University of Florida
4800 SW 35th Drive
Gainesville Florida, 32608
Phone: (352) 265-9900

Samples should be drawn Monday-Wednesday only (except federal holidays) and shipped the same day at room temperature

6.4.8 HLA Determination (Visit -1)

Definition: Human Leukocyte Antigen (HLA) is the name of the major histocompatiblity complex (MHC) in humans. TrialNet will perform immune and genetic assays to further understand mechanisms that may be underlying the Type 1 disease process and response to therapy. HLA testing will be done.

Supplies Needed:

Supply	Collection/Shipment
1 x 6mL lavender top barcode labeled EDTA collection tube	Collection / Shipment
Alcohol Proof Pen	Collection
Styrofoam tube holder with an absorbent pad	Shipment
Cardboard sleeve	Shipment
Bioharzard Ziploc Bag	Shipment
FedEx Diagnostic Specimen Envelope	Shipment
Pre-Printed FedEx Airbill	Shipment

Procedure:

Step 1. Collect Specimen

a. Label one 6 mL lavender top labeled EDTA collection tube with the specimen type (HLA).
b. Scan the one 6mL lavender top labeled EDTA collection tube into the SCF. Write the first three letters of the participant's name and the date of draw (MM/DD/YYYY) with an alcohol-proof pen on the tube or on a label; apply label vertically
c. Draw 5 mL blood into the 6mL lavender top labeled EDTA collection tube and gently invert the tube 8-10 times. DO NOT CENTRIFUGE.
d. Keep the sample at room temperature and ship as whole blood.

Step 2. Complete e-CRF specimen collection form

Step 3. Use shipment system to ship specimens

Step 4. Shipment of HLA

a. Place the tube of whole blood into a Styrofoam tube holder with an absorbent pad.
b. Place the tube holder into a cardboard sleeve and then into a biohazard Ziploc bag.

c. Place the shipment manifest of this completed form in the outside sleeve of the bag.
d. Place the bag into a FedEx Diagnostic Specimen Envelope.
e. Prepare and print a pre-paid airbill to FedEx all samples Priority Overnight to:

Attention HLA/DNA Lab
Barbara Davis Center
1775 Aurora Ct, UC Denver, AMC
M20-4201E
Aurora, CO 80045
Phone: 303-724-6809

Ship specimens Monday - Thursday only (except days before a U.S. federal holiday)

6.4.9 ITN Sample Collection- Whole blood (Visit -1, 0, 1-6, 8, 10)

ITN Whole Blood is collected for Mechanistic Assessment for this study. The whole blood is the PBMC and Plasma.

Procedure and Shipment: To be provided by ITN

6.4.10 ITN Sample Collection- RNA (Visit 0, 2-6, 8, 10)

Definition: RNA: A polymeric constituent of all living cells and many viruses, consisting of a long, usually single-stranded chain of alternating phosphate.

Procedure and Shipment: To be provided by ITN

6.4.11 HbA1c (Visit 0, 4, 6-10)

Definition: HbA1c is a test that measures the amount of glycated hemoglobin in your blood. HbA1c is metabolic assessment that will reviewed. This is part of the diabetes control and will be evaluated every 3 months.

Supplies Needed:

Supply	Collection/Shipment
1 x 1.2 mL lavender top barcode labeled EDTA collection tube	Collection / Shipment
Alcohol-proof pen	Collection/Shipment
Styrofoam Tube Holder with absorbent Pad	Shipment
Cardboard Sleeve	Shipment
Biohazard Ziploc Bag	Shipment
Cold Packs	Shipment
Styrofoam Shipping Container	Shipment
Tape	Shipment
Label: Diamond UN 3373 Biological Specimen Category B	Shipment
Pre-printed FedEx Airbill	Shipment

Procedure:

Step 1. Collection of HbA1c

a. Label one 1.2 mL lavender topped EDTA collection tube with the specimen type HbA1c
b. Scan the one 1.2 mL lavender top labeled EDTA collection tube into the SCF. Write the first three letters of the participant's name and the date of draw

(MM/DD/YYYY) with an alcohol-proof pen on the tube or on a separate label; apply the label vertically

c. Draw 1.2 mL of blood into the 1.2 mL lavender top collection tube and gently invert the tube 8-10 times to mix the sample. **DO NOT CENTRIFUGE**.
d. Keep tube on ice or in refrigerator (4ºC). Ship as whole blood.

Step 2. Complete e-CRF specimen collection form

Step 3. Use shipment system to ship specimens

Step 4. Shipment of HbA1c
a. Place the collection tube into a Styrofoam tube holder with an absorbent pad.
b. Place the Styrofoam tube holder into a cardboard sleeve and then into a biohazard Ziploc bag.
c. Place the shipping manifest of this completed form in the outside sleeve of the bag.
d. Ship sample with cold packs in a Styrofoam shipping container.
e. Tape outer box securely closed.
f. Affix the following label to the outside of the box:
1. Diamond UN 3373 Biological Specimen Category B
g. Prepare and print a pre-paid airbill to FedEx all samples Priority Overnight to:

Specimen Processing
Northwest Lipid Research Laboratories
401 Queen Anne Avenue North
Seattle, WA 98109-4517
Phone: (206) 685-3327

Ship specimens Monday-Thursday only (except days before a U.S. federal holiday)

6.4.12 Cellular Immunoblot (Visit 0 & 5)

This is a mechanistic sample that TrialNet will be assessing.

Supplies Needed:

Supply	Collection/Shipment
2 x 10 mL green top Na Heparin barcode labeled collection tubes	Collection / Shipment
Alcohol proof pen	Collection
Styrofoam tube holder with absorbent pad	Shipment
Cardboard sleeve	Shipment
Biohazard Ziploc Bag	Shipment
Cold Packs	Shipment
Styrofoam Shipping Container	Shipment
Tape	Shipment
Label: Diamond UN 3373 Biological Specimen Category B	Shipment
Pre-printed FedEx Air bill	Shipment

Procedure:

Step 1. Collection of Cellular Immunoblot

Note: At the start of the study: For children <23 kg: No Cellular Immunoblot specimen will be collected.

a. For all other participants: Label two 10 mL green top Na Heparin barcode labeled collection tubes with the specimen type (BLOT).
b. Scan the two 10 mL green top Na Heparin barcode labeled collection tubes into the SCF. Write the first three letters of the participant's name and the date of draw (MM/DD/YYYY) with an alcohol-proof pen on the tube or on a label; apply label vertically
c. Draw two 10mL of blood into the two 10 mL green top Na Heparin barcode labeled collection tubes and immediately gently invert the tubes 8-10 times to mix the samples. **DO NOT CENTRIFUGE.**
d. If the tubes are not packaged for shipping immediately, place tubes at **ROOM TEMPERATURE.**
e. Ship as whole blood PRIORITY OVERNIGHT Monday – Wednesday.
f. **SAMPLES MUST BE SHIPPED ON THE DAY OF THE BLOOD DRAW!!**

Step 2. Complete e-CRF specimen collection form

Step 3. Use shipment system to ship specimens

Step 4. Ship Cellular Immunoblot

a. Place the collection tubes of whole blood into a Styrofoam tube holder with an absorbent pad. Tape the holder securely closed.
b. Place the Styrofoam tube holder into a cardboard sleeve and then into a biohazard Ziploc bag.
c. Place the shipping manifest in the outside sleeve of the bag.
d. Place the Ziploc bag in a manila envelope.
e. Place 2 cold packs that have been REFRIGERATED in a plastic bag.
f. Ship sample along with the bag of cold packs in a FedEx Clinical Pak.
g. Affix a Diamond UN 3373 Clinical Specimen label to the outside of the pak. Write "Clinical Specimens" above label.
h. Prepare and print a pre-paid airbill to FedEx all samples Priority Overnight to:

VA Medical Center
1660 S. Columbian Way
Building 1, Room 609
Seattle, WA 98108
Phone: (206) 764-2696 or 206-764-2616

i. FAX notice of shipment and FedEx airbill number to 206-764-2615

Ship specimens Monday- Wednesday only

6.4.13 Mechanistic Serum (Visit 0, 1- 3, 5, 8, 10)

Mechanistic Serum is collected for mechanistic assessments of antibodies produced by the individual's immune system for this study.

Supplies Needed:

Supply	Collection/Shipment
• 1 x 2.6 mL SST Gel Tube with Clotting Activator, Sarstedt • *2 x 2.6 .6 mL SST Gel Tube with Clotting Activator, Sarstedt (Visit 8 & Visit 10 only)	Collection
• 2 x 2 mL etched centrifuge tubes with O-ring screw caps	Shipment

• *4 x 2 mL etched centrifuge tubes with O-ring screw caps (Visit 8 & Visit 10 only)	
Alcohol –Proof Pen	Collection/Shipment
3" partitioned freezer storage box	Shipment
Biohazard Ziploc Bag with absorbent sheet	Shipment
Large Styrofoam shipping container	Shipment
Dry Ice at least 5lbs or 3kg	Shipment
Tape	Shipment
Labels: • Black Diamond UN1845 Dry Ice Label • Diamond UN 3373 Biological Specimen Category B Label	Shipment
Prepaid FedEx Airbill	Shipment

Note: Mechanistic Serum will be collected twice as much for only visits Visit 8 & Visit 10

Procedure:

Step 1. Collect Specimen

a. Label one 2.6 mL SST Gel Tube with Clotting Activator, Sarstedt with the specimen type (MECHANISTIC SERUM).
   i. *Note: For visit 8 and Visit 10 only, label two 2.6 mL SST Gel Tube with Clotting Activator, Sarstedt with specimen type (MECHANISTIC SERUM)
b. Scan two 2 mL etched centrifuge tubes with O-ring screw caps into the SCF. (*For visit 8 and visit 10 only scan 4 2mL etched centrifuge tubes with O-ring screw caps) Write the first three letters of the participant's name and the date of draw (MM/DD/YYYY) with an alcohol-proof pen on the tube or on a separate label; apply the label vertically
c. Draw 2 mL of blood into one 2.6 mL Gel Tube with Clotting Activator, Sarstedt.
   i. *Note: For Visit 8 and Visit 10 only, draw two 2mL of blood into 4 2.6mL Gel Tube with Clotting Activator, Sarstedt.
d. Gently invert tube 5 times and place upright in a tube rack. Allow blood to clot for 20-30 minutes at room temperature (65 º-75º F).
e. Centrifuge at full speed for 15 minutes.
f. Transfer equal volumes of serum into two 2mL centrifuge tubes with O-ring screw caps. Screw top on tightly.
   i. *Note: For visit 8 and Visit 10 only, transfer equal volumes of serum into four 2mL centrifuge tubes with O-ring screw caps.
g. Place samples upright in a 3" partitioned freezer storage box. Freeze at -20º C.
h. If shipping unfrozen same day, skip step 4 and refer to step 5

Step 2. Complete e-CRF specimen collection form

Step 3. Use shipment system to ship specimens

Step 4. Shipment of Mechanist Serum specimens **frozen**

a. Ship batched frozen samples weekly.
b. Place the 3" partitioned freezer storage box with samples into a biohazard Ziploc bag with an absorbent sheet.
c. Place a printed copy of the shipment manifest in the outside sleeve of the bag.
d. Place the bag into a large Styrofoam shipping container filled to capacity with dry ice (at least 5 lbs. or 3 kg) and tape outer cardboard box securely closed.
e. Affix the following labels to the outside of the box:
   i. Black Diamond UN1845 Dry Ice Label

ii. Diamond UN 3373 Biological Specimen Category B Label (placed on the same side as the Black Diamond Dry Ice Label).

f. Prepare and print a pre-paid FedEx airbill to ship specimen Priority Overnight to:
TrialNet Core Screening Laboratory (UFDRL)
University of Florida
4800 SW 35th Drive
Gainesville Florida, 32608
Phone: (352) 265-9900

Ship specimens Monday – Thursday only (except days before a United States federal holiday)

Step 5. Shipment of Mechanistic Serum specimens **unfrozen (the SAME DAY)**: Samples should be drawn Monday-Wednesday only (except federal holidays) and shipped the same day at room temperature if shipped unfrozen.

a. Place tubes into a Styrofoam tube holder with an absorbent pad.
b. Place the tube holder into cardboard sleeve and into the biohazard Ziploc bag
c. Place the shipment manifest into the outside pocket of the bag.
d. Please the bag into a FedEx Diagnostic Specimen Envelope and ship to:
TrialNet Core Screening Laboratory (UFDRL)
University of Florida
4800 SW 35th Drive
Gainesville Florida, 32608
Phone: (352) 265-9900

6.5 Subject Transfer

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

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.

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 Pregnancy

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. 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, withdrawals consent, or becomes lost to follow up 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 6. 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 7. Complete the "Pregnancy Confirmation" e-CRF PRN form. See section 9.6 for instructions on how to access PRN forms

Step 8. If there is remaining study drug, ship the remainder drug back to the central pharmacy. Refer to the pharmacy manual for instructions on agent return.

Step 9. Fulfill any local reporting requirements (IRB, GCRC, ect)

Step 10. Notify TNCC of any concerns or questions.

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.

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.

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.

7.1.4 Completion of All Required Areas

All signature, date, checkboxes, and initial lines must be completed by the subject, subject's representative or guardian, witness, trial coordinator, and investigator where applicable. 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
  - Ensure **Stored Samples** section is completed by the participant (check boxes and subject initials)
- Interventional Consent- to be signed by the participant and others (witness, investigator, trial coordinator) as applicable

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.
  - Ensure **Stored Samples** section is completed by the participant's guardian/representative (check boxes and subject initials)
- 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.
- Interventional Assent- to be signed by the child/participant and others (witness, investigator, trial coordinator) as applicable.

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

8.1 Introduction

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

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

The TNCC uses a system of coded identifiers to protect participant confidentiality and safety. Each participant enrolled is assigned a local identifier by the enrollment site. Only the registering site will have access to the linkage between this number and the personal identifier of the participant. When the participant is registered in the study, using the TNCC provided web-based registration system, the system will assign a 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.

8.2 Protocol Tool Management

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

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

8.3 System Requirements

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

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

General considerations when using a web-based system

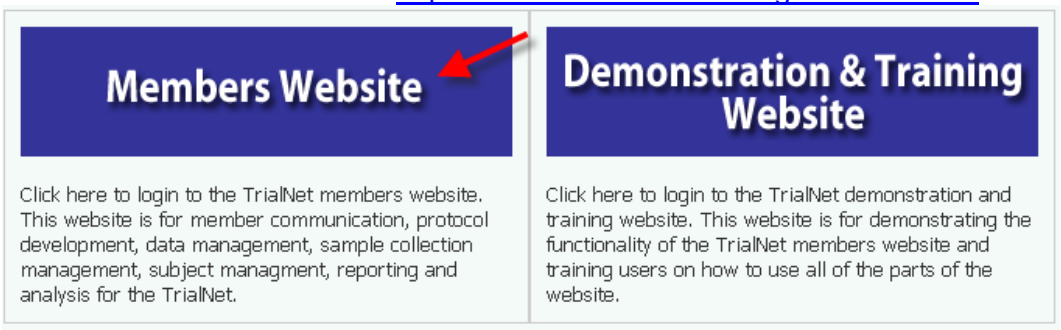
- You can access this system from any machine that has the hardware and software described above, no special installation is required.
- No intensive training needed to use this application. If you are familiar with the use of a browser you already have the basic knowledge.
- Updates to the system will be done on the server without 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

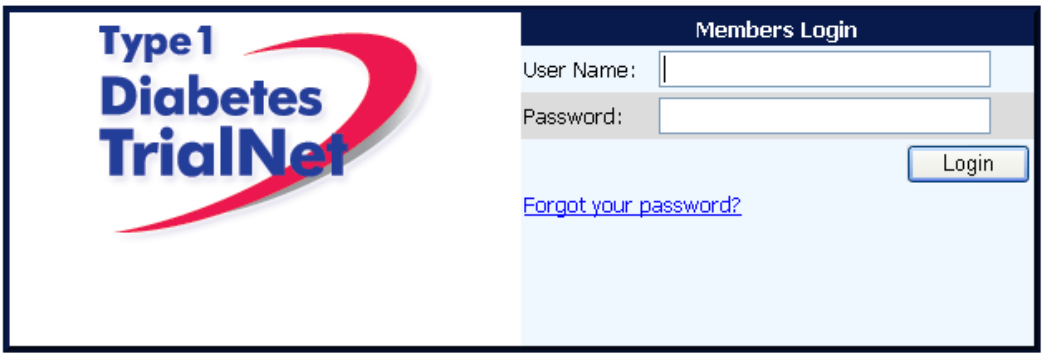
9.1 Overview and Basic Functionality

9.1.1 Login/Navigate to the TN08 Protocol Manager Area

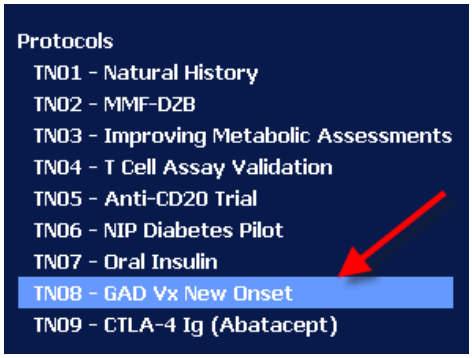
Step 1. Procedure to login and navigate to the TN08 protocol manager area: Log into TrialNet **Members** Site: http://www.diabetestrialnet.org/members.htm



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



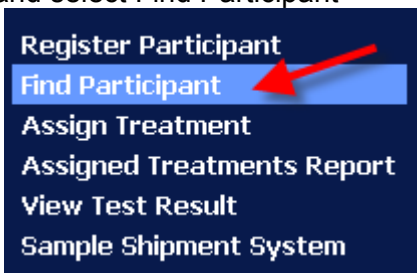
Step 3. Navigate to TN08 Protocol Manager by clicking "TN08 – GAD Vx New Onset" on the left hand navigation bar



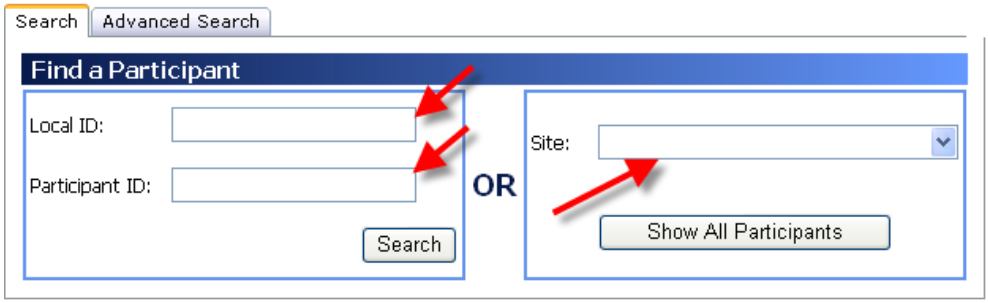
9.1.2 Finding a Participant

Note this procedure will be done for every visit.

Step 1. Procedure to find participant: Once in TN08 Protocol, navigate to the left hand side and select Find Participant

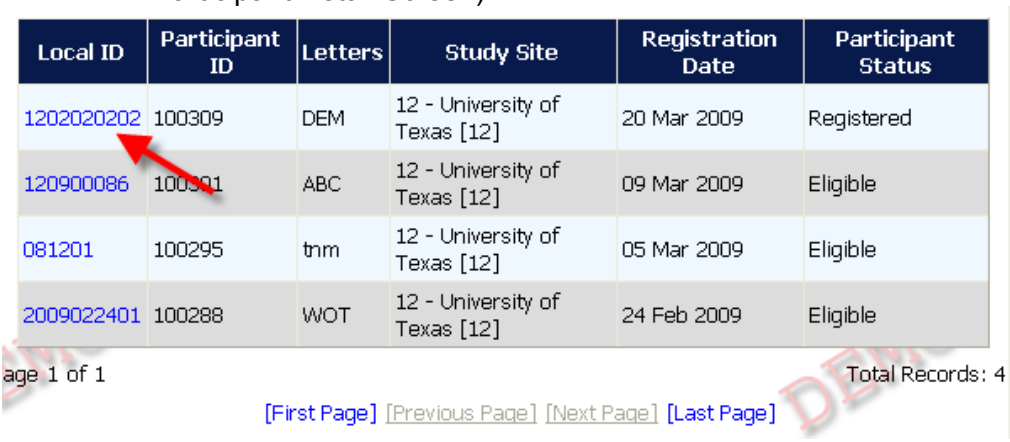


Step 2. Search for Participant (Enter either Local ID or Participant ID or search by site)



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

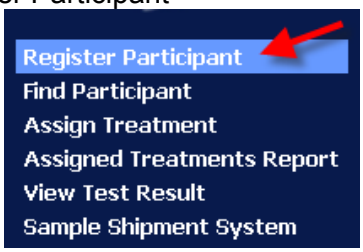
age 1 of 1 Total Records: 4

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

9.1.3 Registering a Participant

Step 1. Procedure Registering a Participant on TN08: Follow Section to Log into TrialNet Members Website and navigate to TN08 protocol manager area (section 9.1.1)

Step 2. Once in TN08 GAD New Onset Home Page, from the left navigation menu select Register Participant



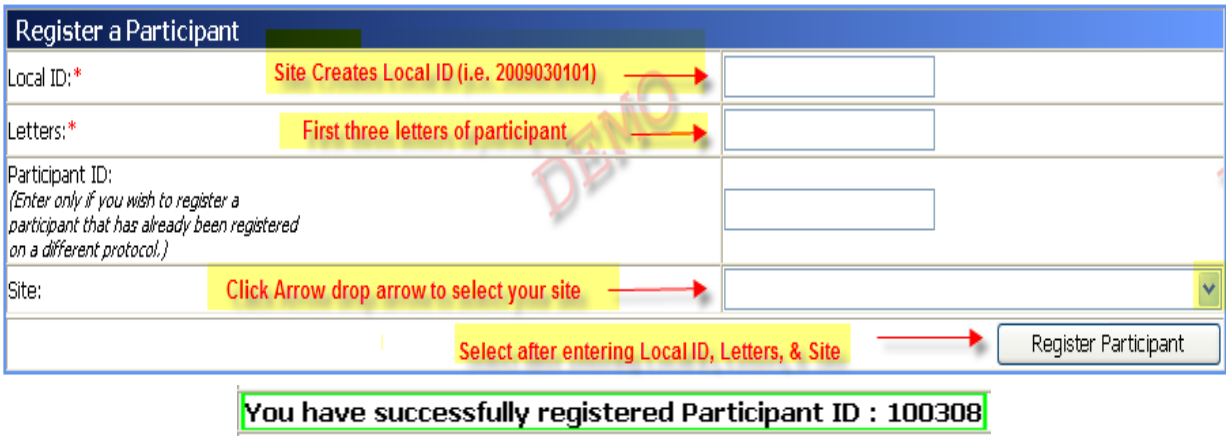
Step 3. Once the Register Participant Screen is displayed complete the following fields

a. Local ID: Create a Local ID (Please refer to section titled Local ID)
b. Enter First Three Letters of Participant's name
c. Participant ID: Can be skipped if first time participant on TrialNet Study

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

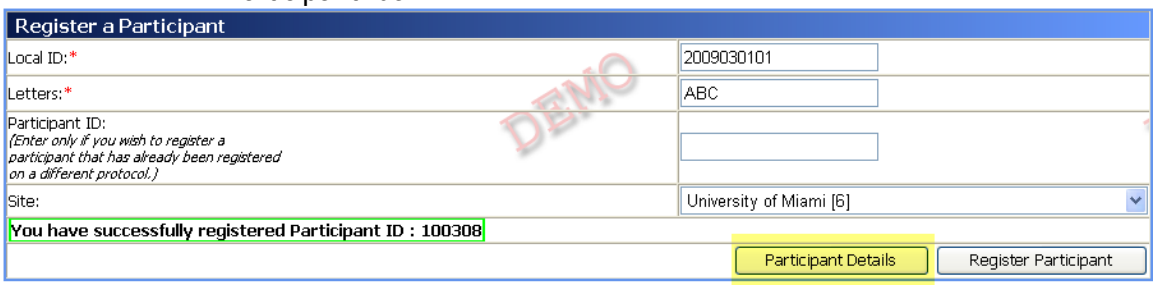
d. Select applicable clinical center

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.

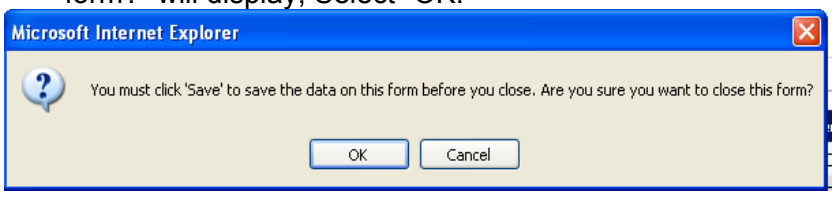


9.1.4 Save and Close e-CRFs

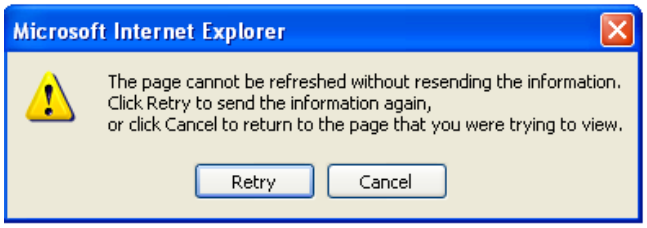
Note: This procedure will be the same after each e-CRF is completed

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."



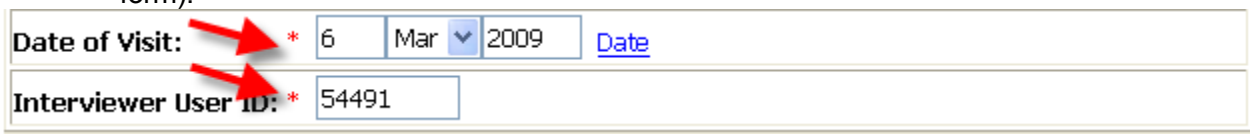
Step 3. The following message will display, "The page cannot be refreshed without resending the information Click Retry to send the information again, or click Cancel to return to the page that you were trying to view." Select Retry and screen will automatically return to Participant Details



9.1.5 Form Required Fields

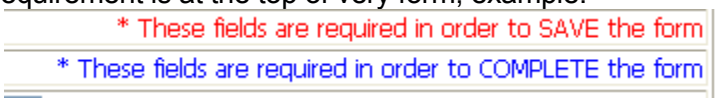
There are two kinds of required fields on every form:

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:

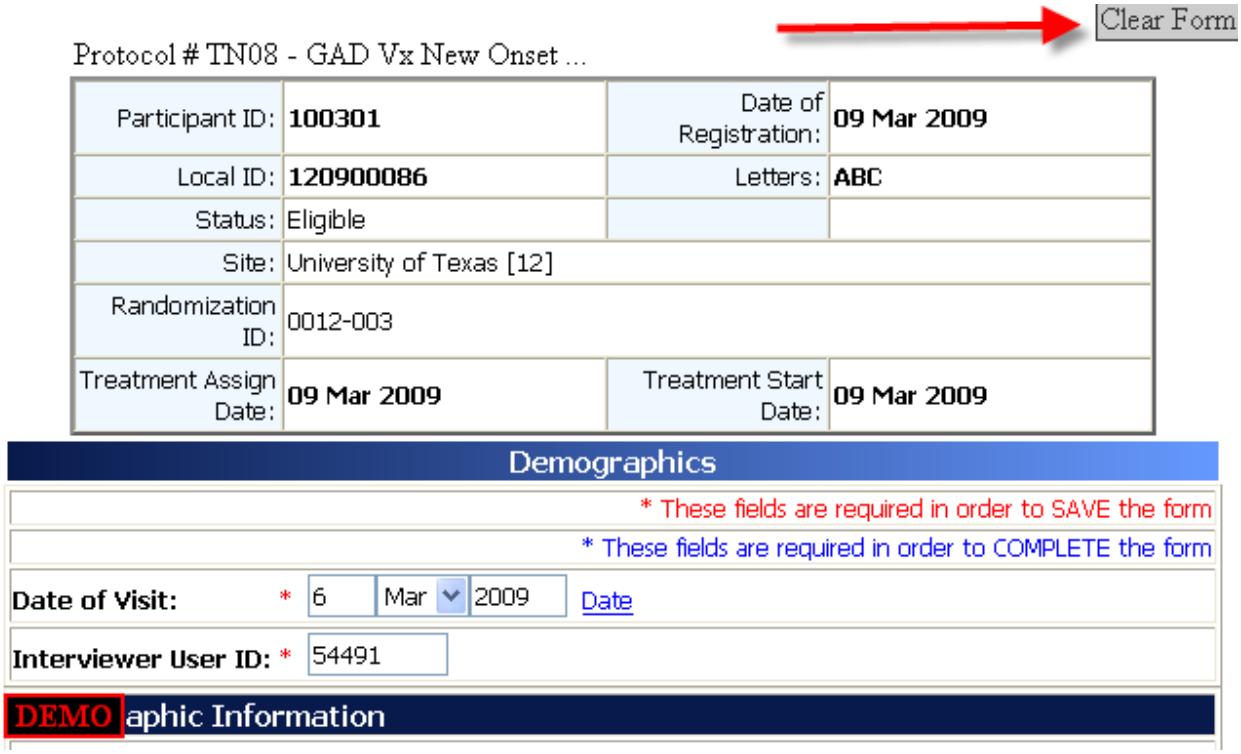


9.1.6 Clear ALL Data from a Form

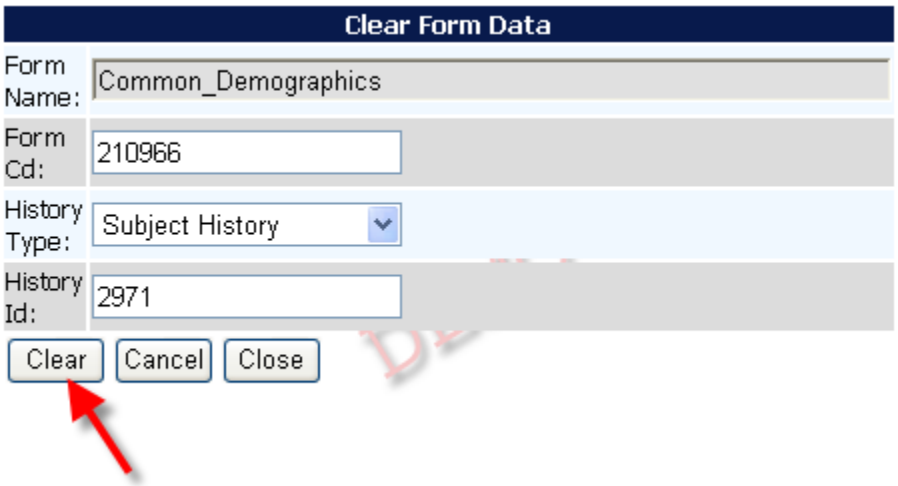
If you find you have mistakenly entered data on the wrong form or wrong data on a form, you can clear all data on the form as long as you are the person who entered the data on the form.

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

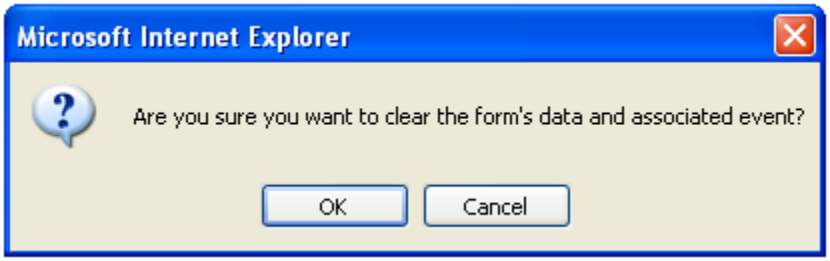
Step 2. Click on the button entitled “Clear Form” in the upper right hand corner of the screen.



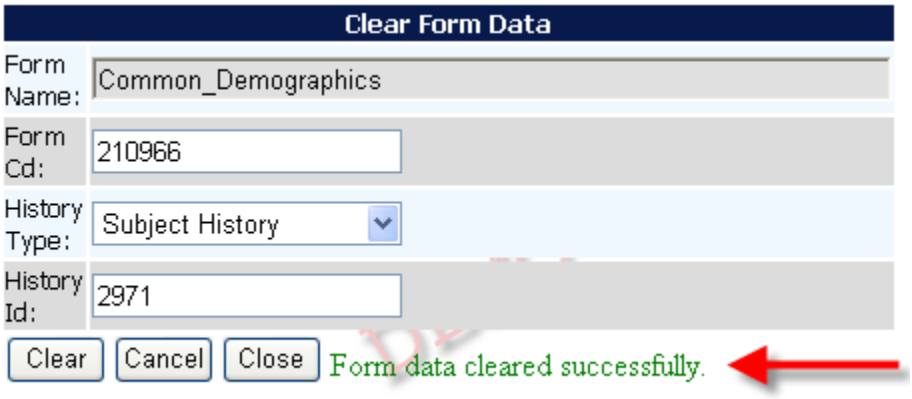
Step 3. The page will navigate to a description of the form you are about the clear (Clear Form Data box). If you are certain you wish to clear out all data on the form, click the button “Clear”



Step 4. A pop-up window will display asking you if you are certain you want to clear the form. If you are certain, click “Ok”



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



Step 6. Click the "Close" button and you will navigate back to the participant's details.

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** if there are required data elements missing
  - If the status is **Complete** all required data elements have been entered and the form has been saved (fields on the form with blue asterisks).

9.3 Screening Visit

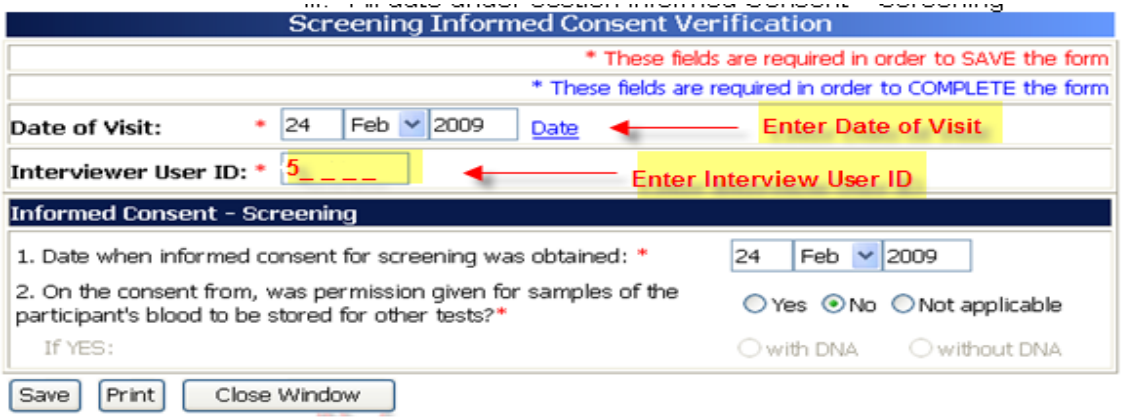
9.3.1 Screening Informed Consent Verification

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

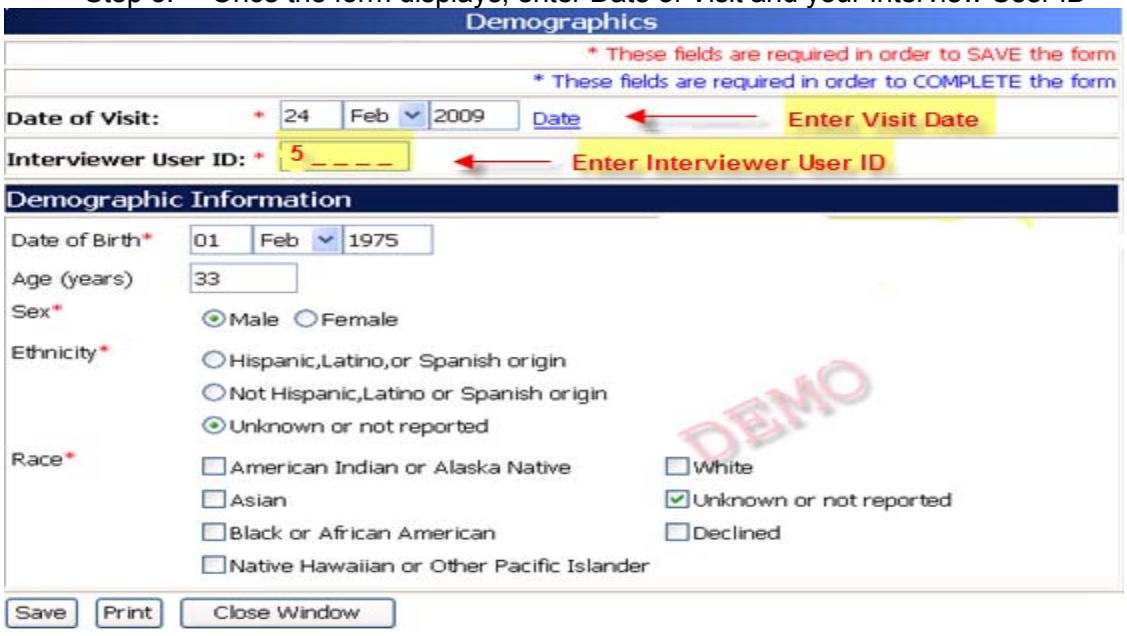
Step 5. After entering data, please reference section 9.1.4 Save and Close e-CRF form.

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

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



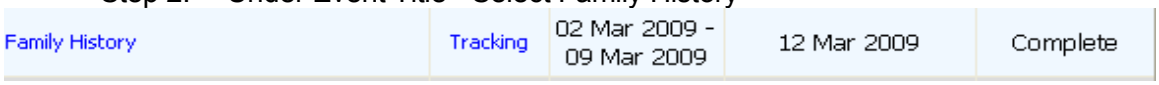
Step 4. Complete Demographics Information Section

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

9.3.3 Family History

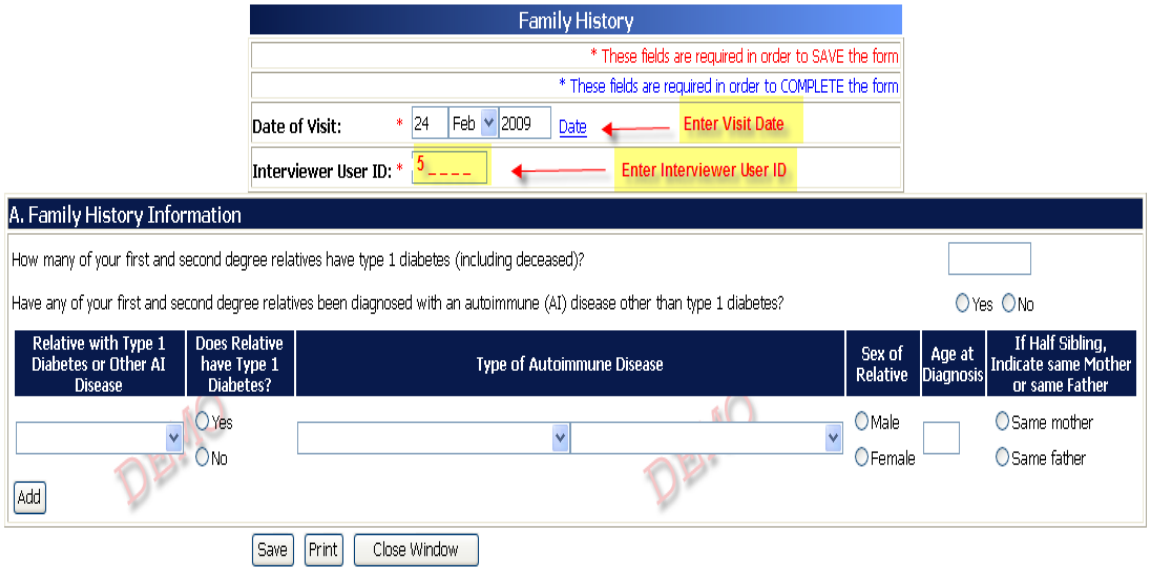
Step 1. Procedure to enter data for Family History: Be sure the Source Document is completed prior to completing forms

Step 2. Under Event Title - Select Family History



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

Step 4. Complete Family History Section

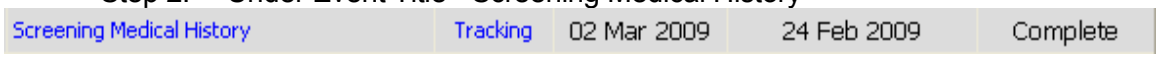


Step 5. After entering data, please reference section 9.1.4 Save and Close e-CRF form.

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



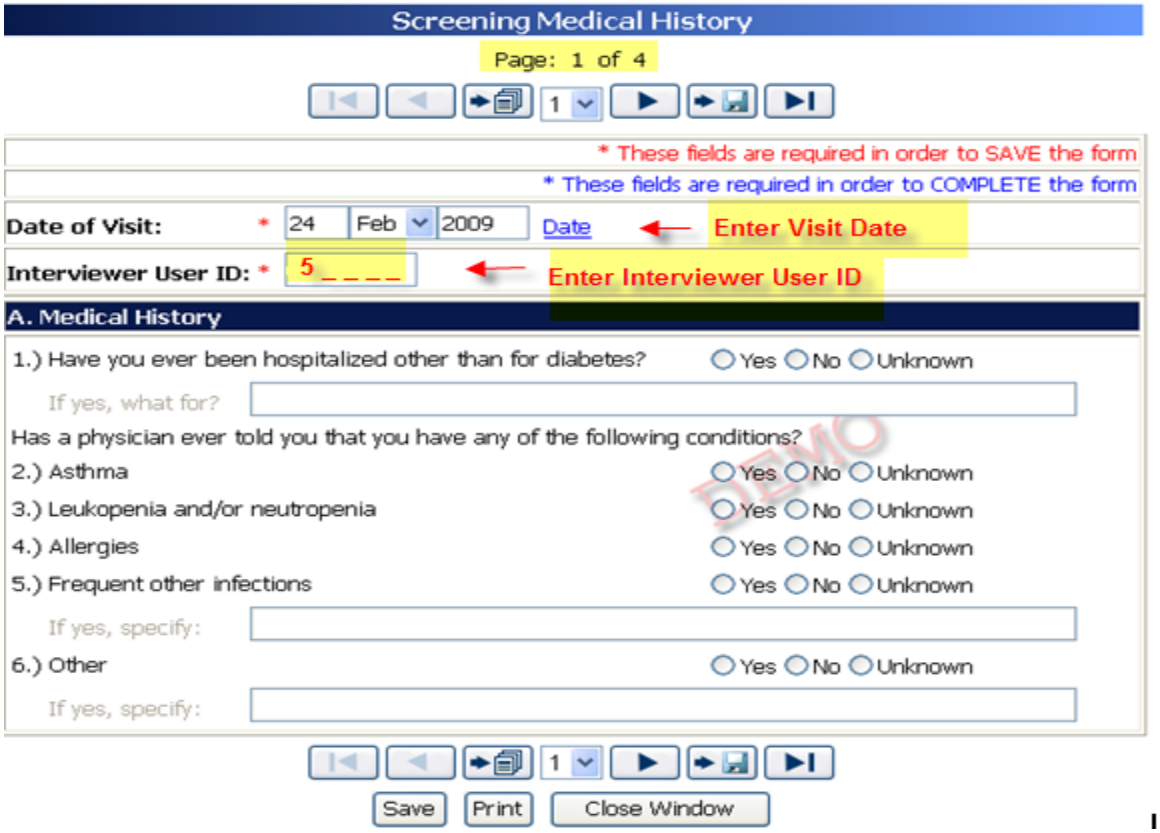
Step 3. Once the form displays, enter Date of Visit and your Interview User ID

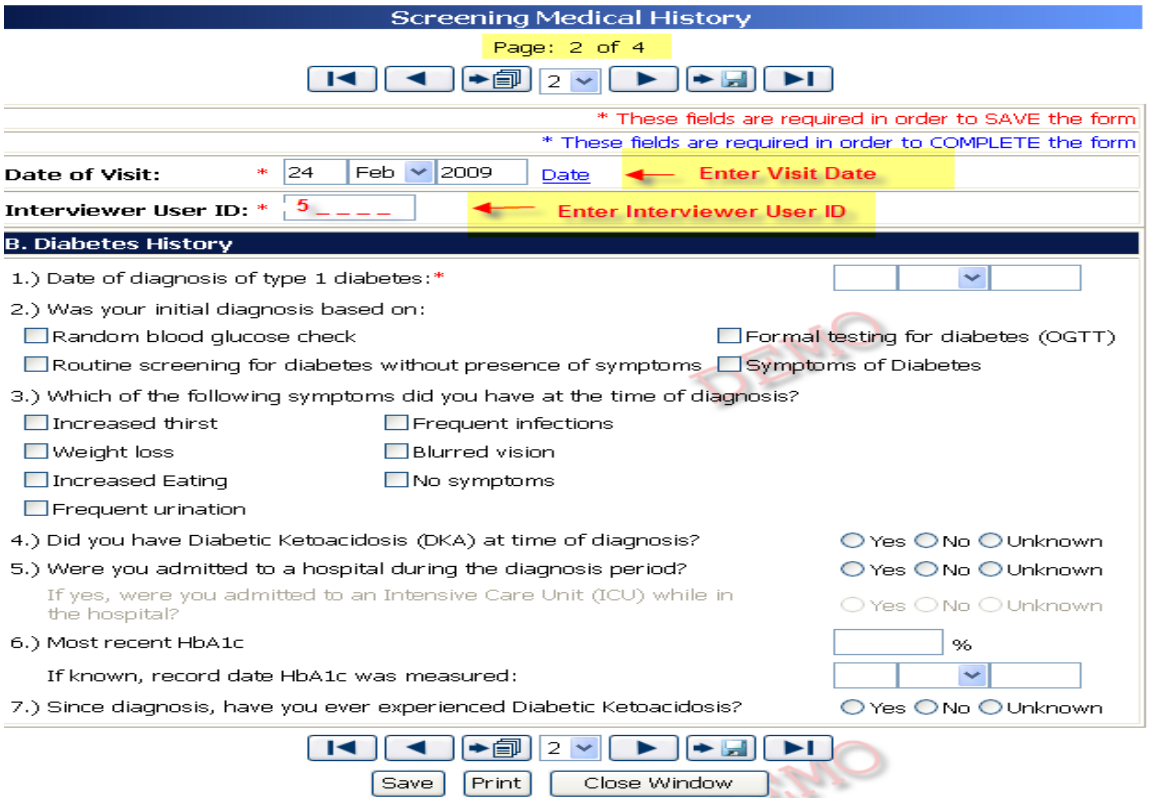
Step 4. Complete all following sections for this form: Note the Screening Medical History Form contains 4 pages.

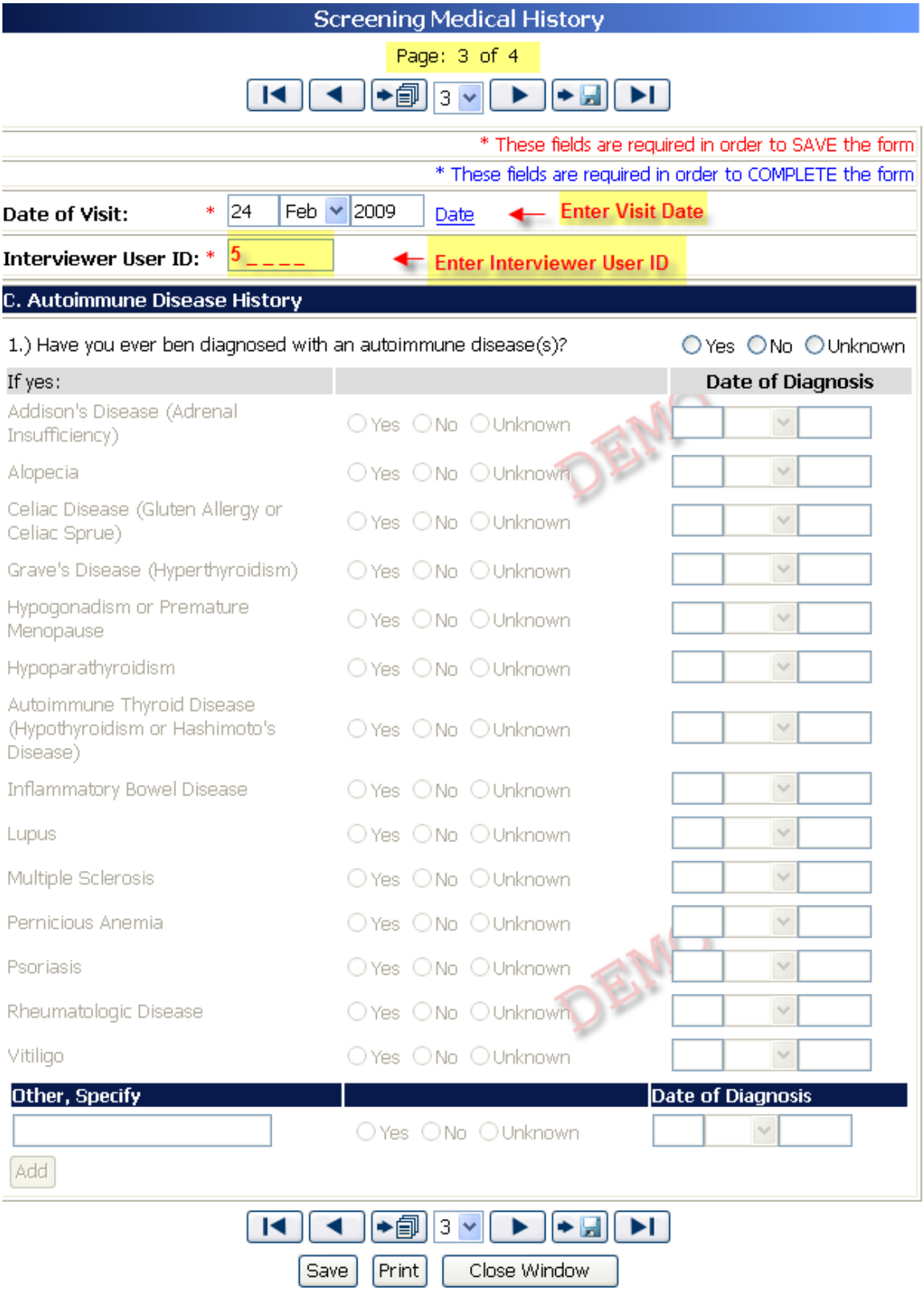
- *a. Section A. Medical History*
  1. *Review if participant has been hospitalized other then for diabetes*
  2. *Review of any condition/disease*
- *b. Section B. Diabetes History*
  1. *Collect information about participant's diabetes history*
  2. *Section C. Autoimmune Disease History*
  3. *Collect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

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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

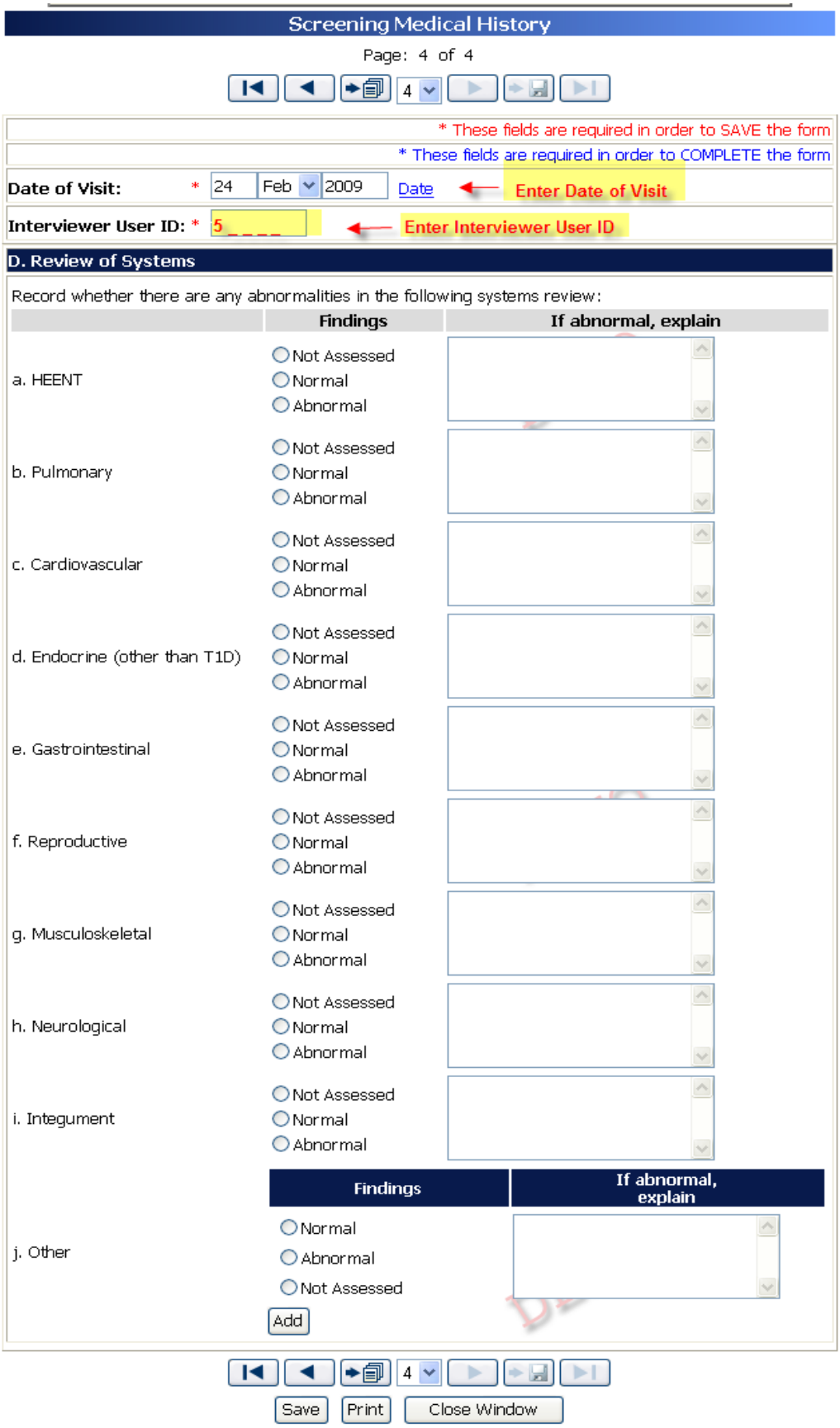
If yes:		Date of Diagnosis
Addison's Disease (Adrenal Insufficiency)	○ Yes ○ No ○ Unknown	
Alopecia	○ Yes ○ No ○ Unknown	
Celiac Disease (Gluten Allergy or Celiac Sprue)	○ Yes ○ No ○ Unknown	
Grave's Disease (Hyperthyroidism)	○ Yes ○ No ○ Unknown	
Hypogonadism or Premature Menopause	○ Yes ○ No ○ Unknown	
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

3

Save Print Close Window



Screening Medical History

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4

* 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 Date of Visit

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

D. Review of Systems

Record whether there are any abnormalities in the following systems review:

	Findings	If abnormal, explain
a. HEENT	○ Not Assessed ○ Normal ○ Abnormal	
b. Pulmonary	○ Not Assessed ○ Normal ○ Abnormal	
c. Cardiovascular	○ Not Assessed ○ Normal ○ Abnormal	
d. Endocrine (other than T1D)	○ Not Assessed ○ Normal ○ Abnormal	
e. Gastrointestinal	○ Not Assessed ○ Normal ○ Abnormal	
f. Reproductive	○ Not Assessed ○ Normal ○ Abnormal	
g. Musculoskeletal	○ Not Assessed ○ Normal ○ Abnormal	
h. Neurological	○ Not Assessed ○ Normal ○ Abnormal	
i. Integument	○ Not Assessed ○ Normal ○ Abnormal	

	Findings	If abnormal, explain
j. Other	○ Normal ○ Abnormal ○ Not Assessed	

Add

4

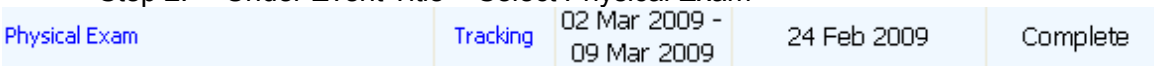
Save Print Close Window

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

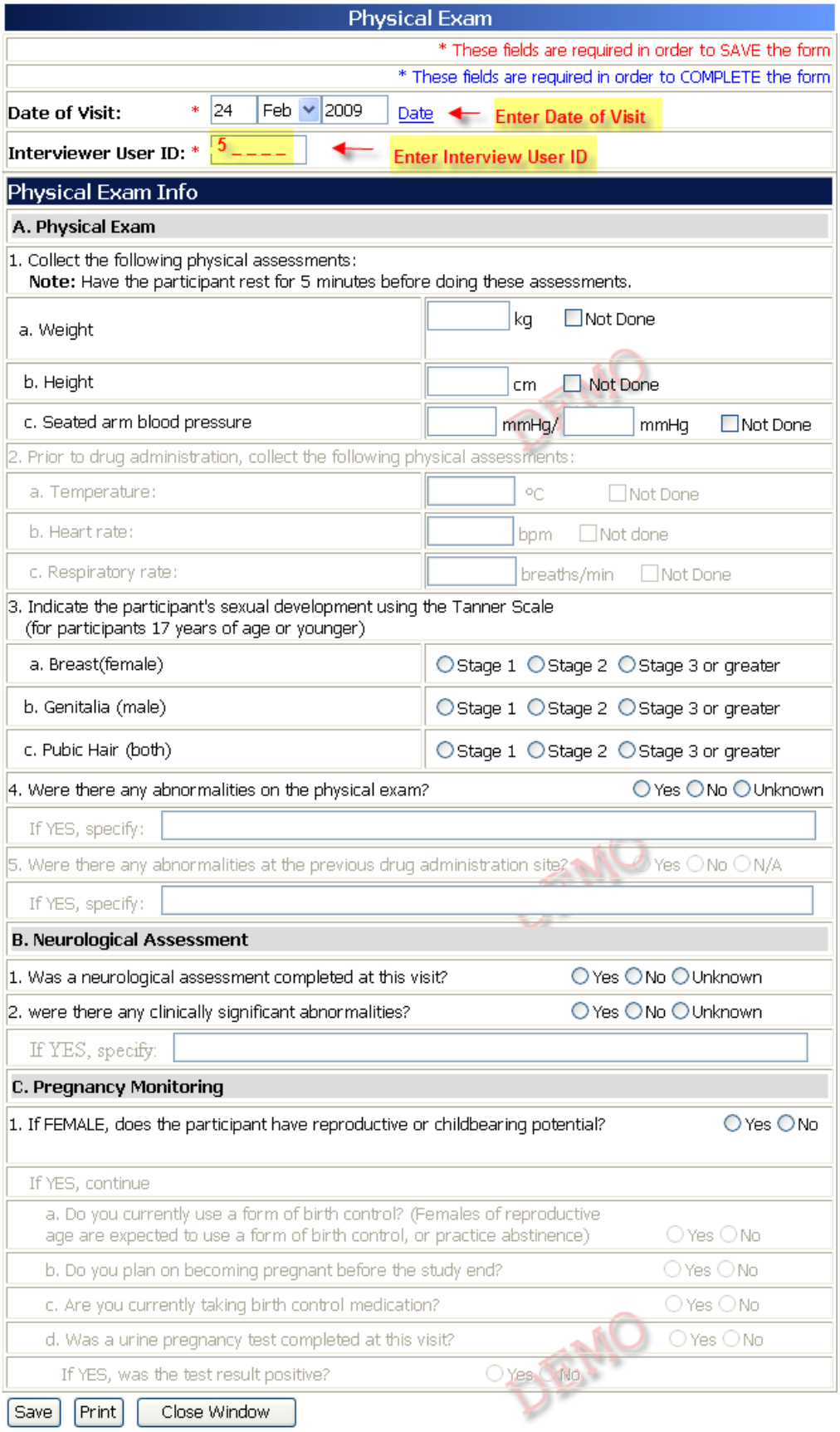


Step 3. When the form displays, enter Date of Visit and your Interview User ID. Complete all following sections for this form:

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

b. *Section B. Neurological Assessment*
   - *Collect information if the participant had any neurological assessments done and if there were any abnormalities.*

c. *Section C. 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.*



Physical Exam

* 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 Date of Visit

Interviewer User ID: * 5____ ← Enter Interview User ID

Physical Exam Info

A. Physical Exam

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

a. Weight	kg Not Done
b. Height	cm Not Done
c. Seated arm blood pressure	mmHg/ mmHg Not Done

2. Prior to drug administration, collect the following physical assessments:

a. Temperature:	°C Not Done
b. Heart rate:	bpm Not done
c. Respiratory rate:	breaths/min Not Done

3. Indicate the participant's sexual development using the Tanner Scale
(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

4. Were there any abnormalities on the physical exam? Yes No Unknown

If YES, specify:

5. Were there any abnormalities at the previous drug administration site? Yes No N/A

If YES, specify:

B. Neurological Assessment

1. Was a neurological assessment completed at this visit? Yes No Unknown

2. were there any clinically significant abnormalities? Yes No Unknown

If YES, specify:

C. Pregnancy Monitoring

1. If FEMALE, does the participant have reproductive or childbearing potential? Yes No

If YES, continue

a. Do you currently use a form of birth control? (Females of reproductive age are expected to use a form of birth control, or practice abstinence) Yes No

b. Do you plan on becoming pregnant before the study end? Yes No

c. Are you currently taking birth control medication? Yes No

d. Was a urine pregnancy test completed at this visit? Yes No

If YES, was the test result positive? Yes No

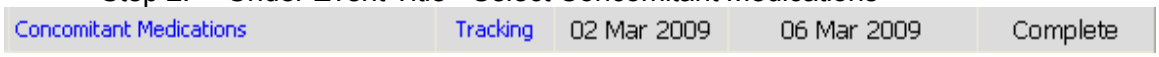
Save Print Close Window

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

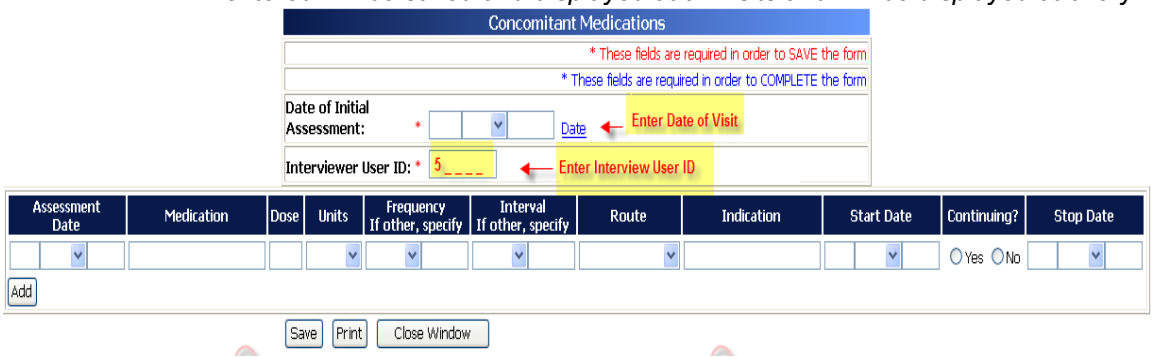
9.3.6 Concomitant Medications

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*



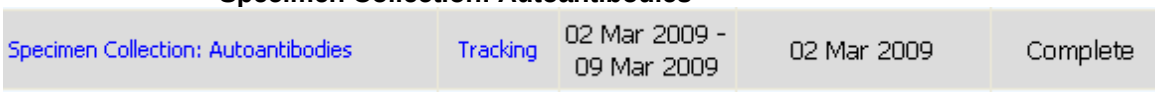
Step 4. After entering data, please reference section 9.1.4 Save and Close e-CRF form

9.3.7 Specimen Collection Forms: Autoantibodies, Chemistries, EBV/CMV, HIP/HepB/HepC, HLA

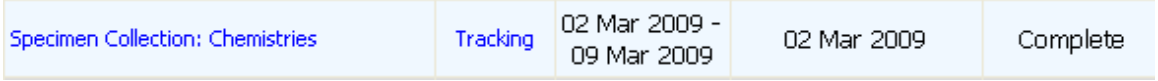
Step 1. The following procedures will be the same for each specimen listed above. Be sure the Source Document is completed prior to completing the Specimen Collection Form

Step 2. Under Event Title: Select Applicable Specimen Collection Form. Forms that would be included in this procedure are:

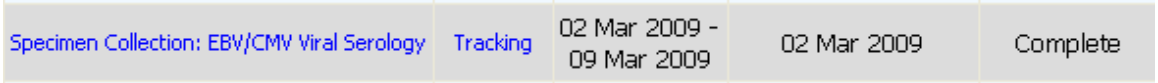
- **Specimen Collection: Autoantibodies**



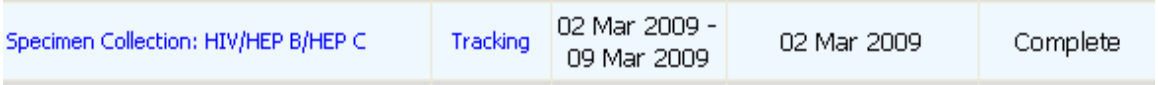
- **Specimen Collection: Chemistries**



- **Specimen Collection: EBV/CMV Viral Serology**



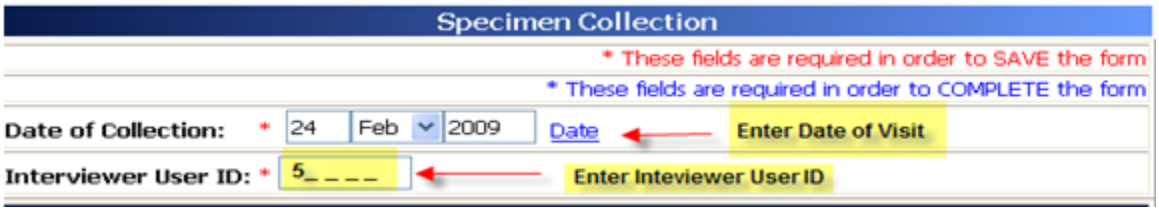
- **Specimen Collection: HIV/HEPB/HEPC**



- **Specimen Collection: HLA**

Specimen Collection: HLA	Tracking	02 Mar 2009 - 09 Mar 2009	02 Mar 2009	Complete

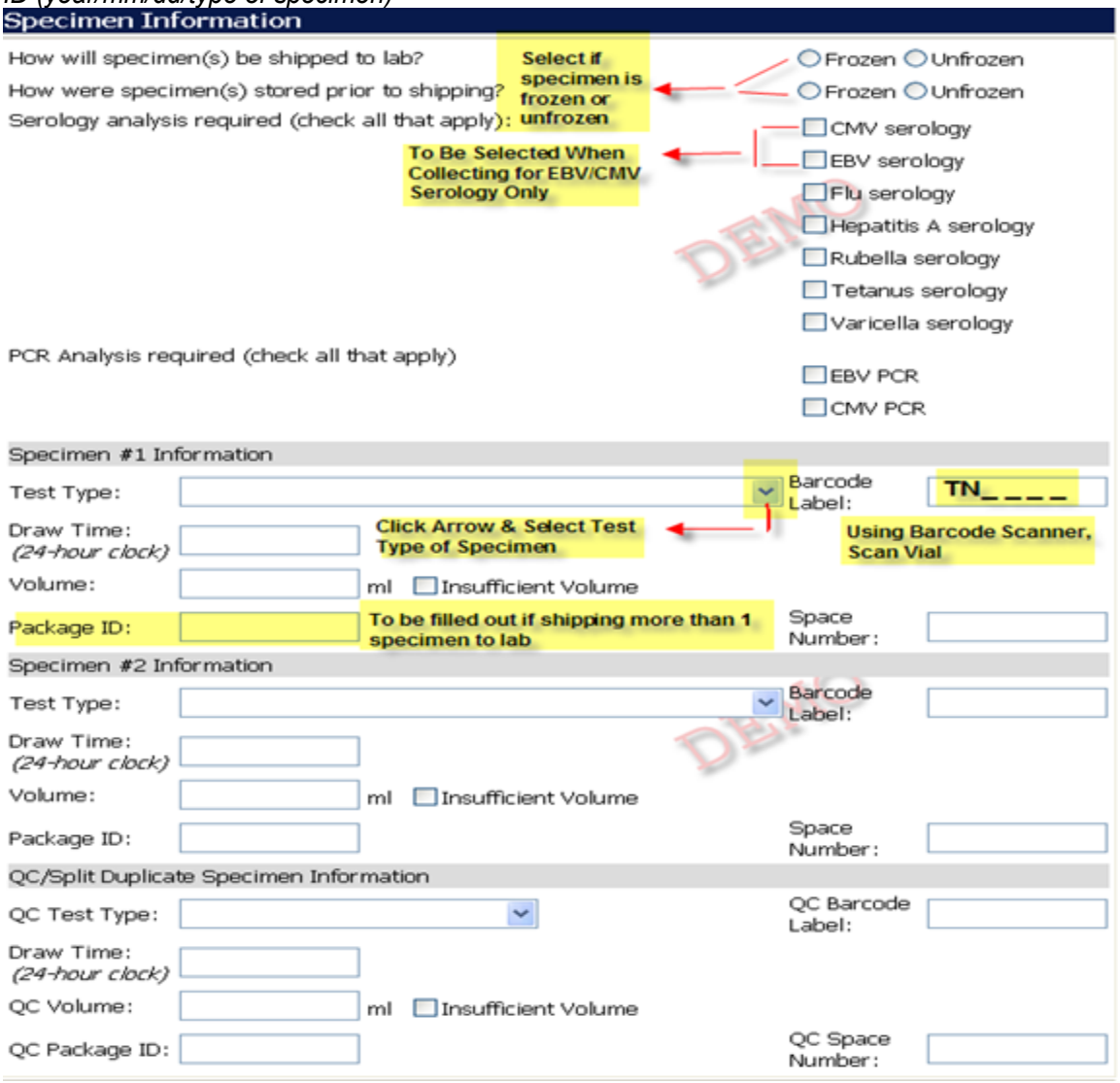
Step 3. Once the form displays, enter Date of Visit and Interview User ID



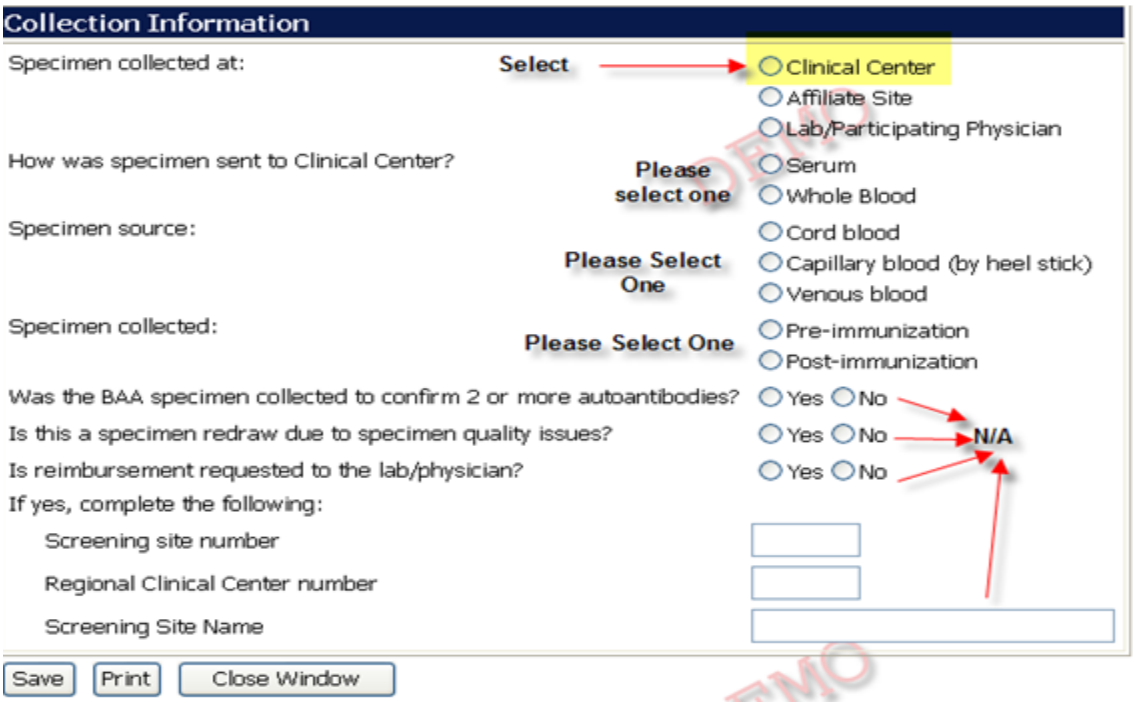
Step 4. Complete Specimen Information

i. Complete how specimen will be shipped to lab
ii. Select Test Type: Lab Specimen as listed above
iii. 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



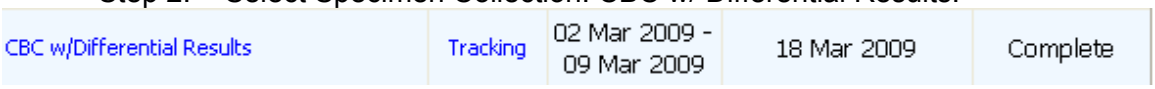
Step 6. After entering data, please reference section 9.1.4 Save and Close e-CRF form.

Step 7. Proceed to next 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

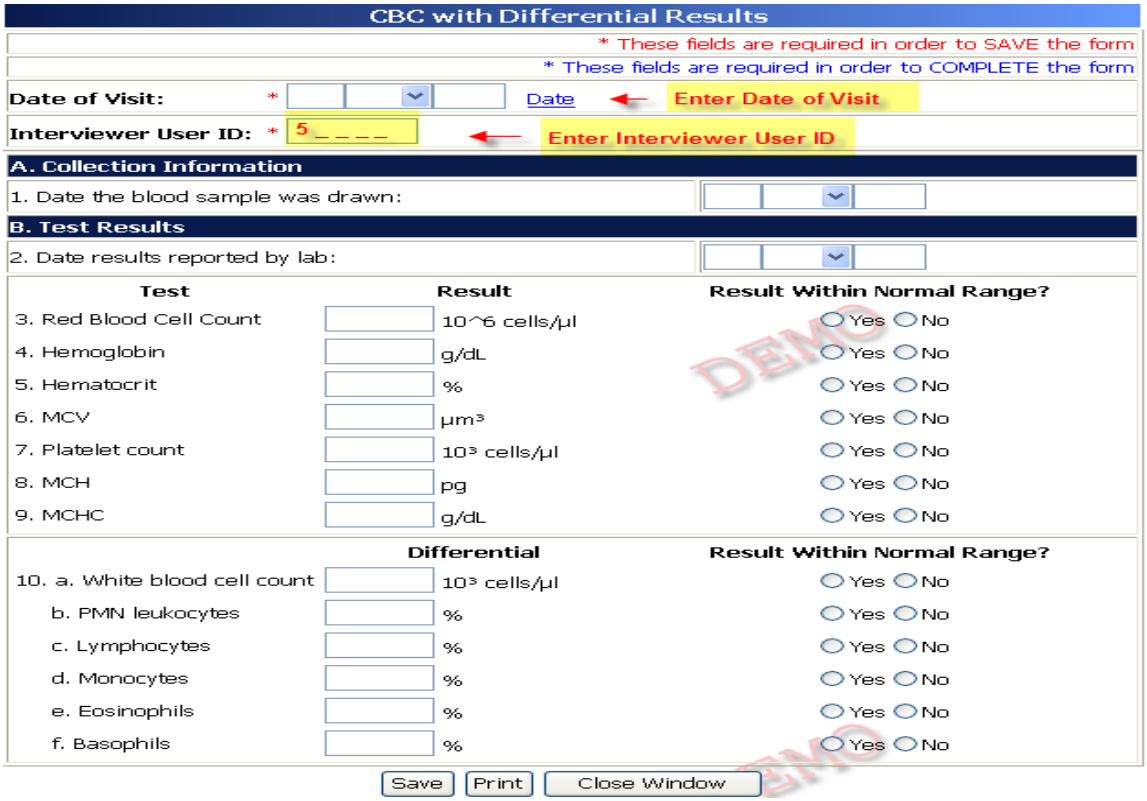
Step 2. Select Specimen Collection: CBC w/ Differential Results:



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



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

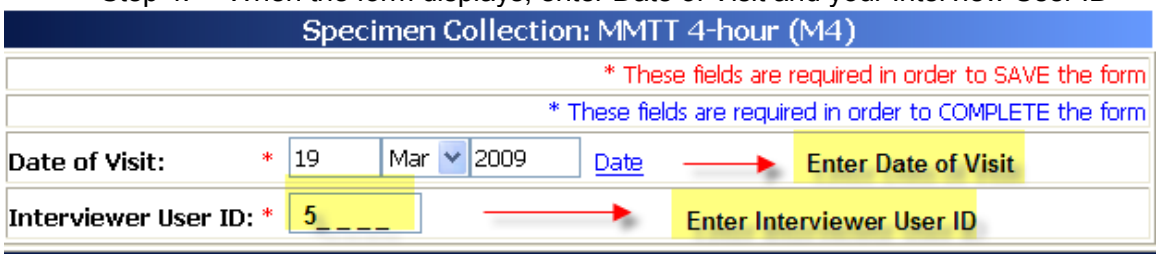
9.3.9 4-hr MMTT / 2-hr MMTT

Step 1. Procedure to complete the MMTT Specimen Collection Form: Be sure the Source Document is completed prior to completing this specimen collection form.

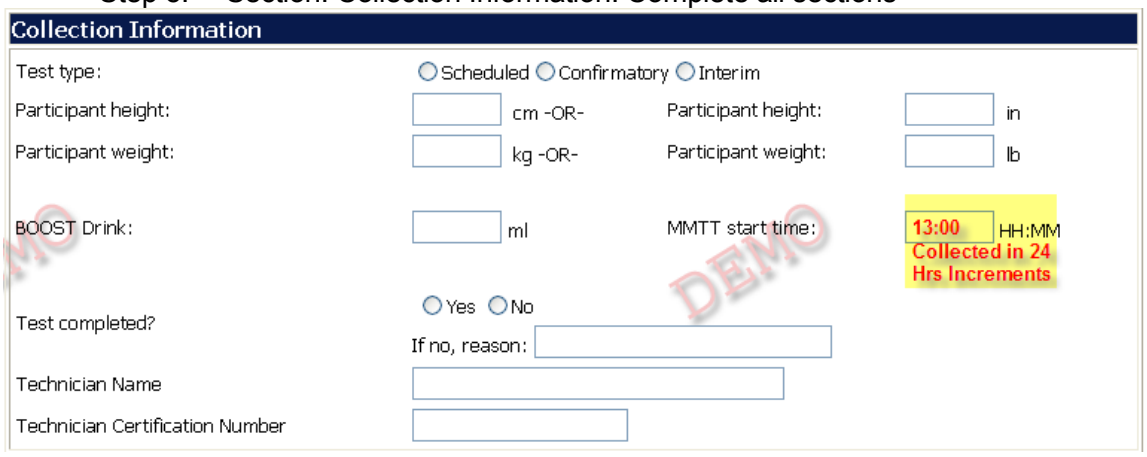
Step 2. For the screening visit, the demographics form must be completed prior to entering data on the MMTT specimen collection form.

Step 3. Select the MMTT Form (the MMTT form that displays depends on data entered in the demographics form; a 4-hr MMTT form will display if the subject is older than 12; a 2-hr MMTT form will display if the subject is 12 or younger.)

Step 4. When the form displays, enter Date of Visit and your Interview User ID



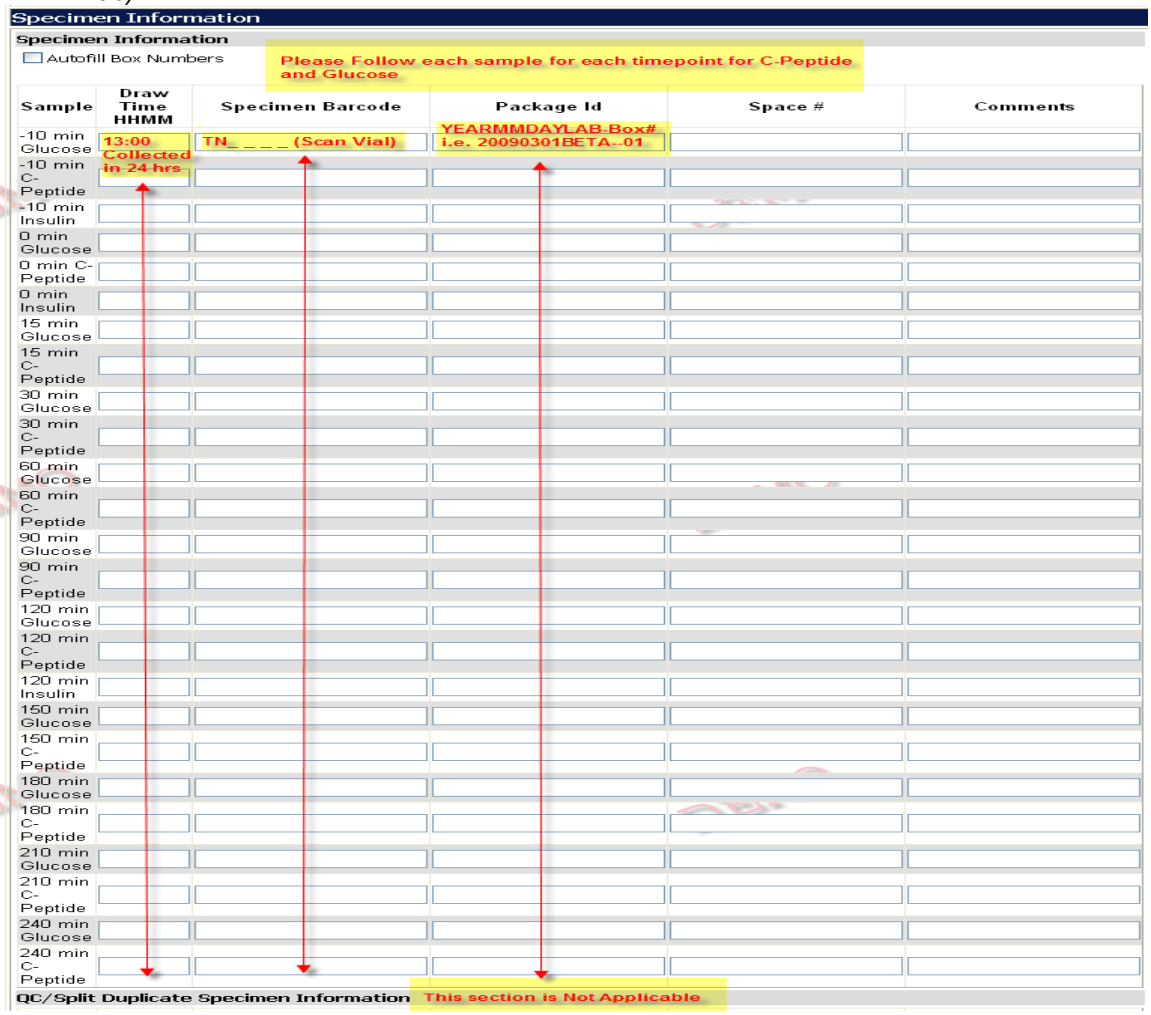
Step 5. Section: Collection Information: Complete all sections



Step 6. Section Specimen Information: This form is collecting date for each Glucose and C-Peptide time points.

Step 7. Using the scanner begin scanning each of the vials.

Enter a Package ID. For example: 20090220MMTT (year/mm/dd/type of specimen to be sent to lab)



Note: No Need to complete QC/Split Duplicate Specimen Information Section

Step 8. 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.

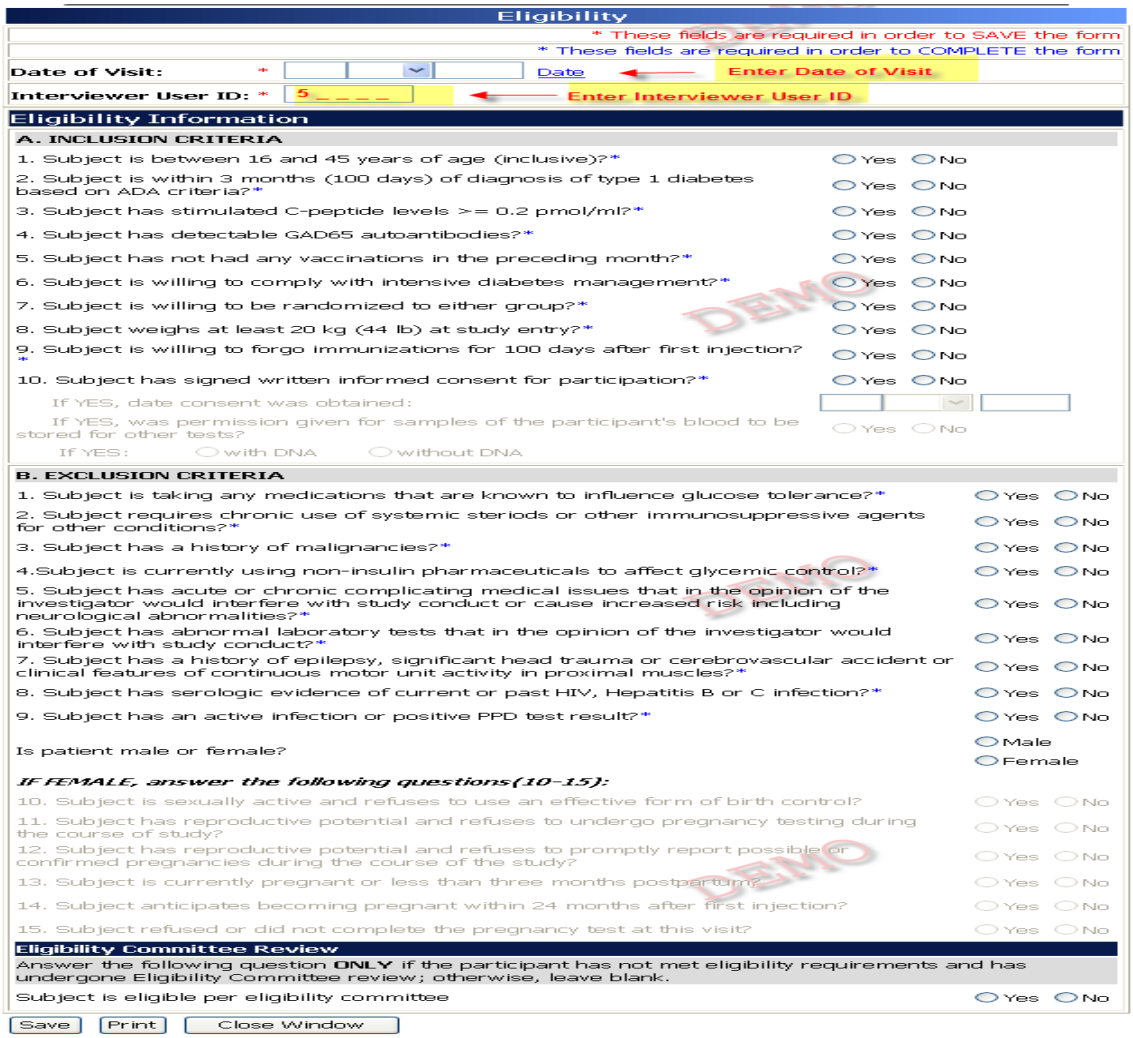
Step 1. Procedure to complete eCRF Eligibility: Be sure the Source Document is completed prior to completing this specimen collection form.

Step 2. Under the Event Title select: Eligibility

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

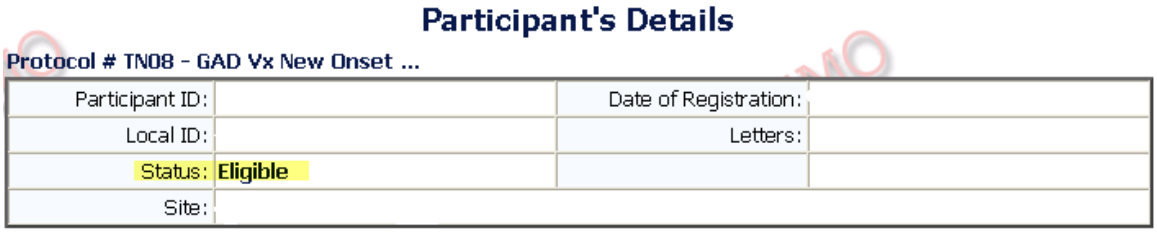
Step 4. Complete the following sections:

a. Section A. Inclusion Criteria
b. Section B. Exclusion Criteria



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.



9.4.2 Randomizing a Participant in the System

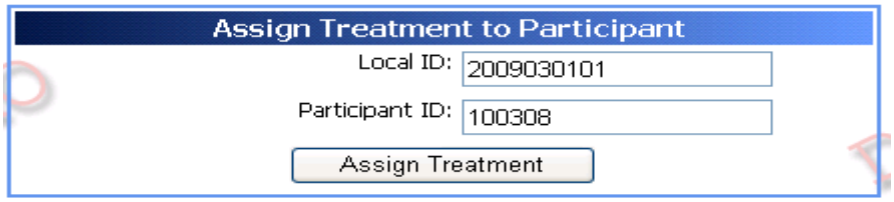
Step 1. Procedure to assign treatment and obtain randomization number: *the **Eligibility form must be complete** and the subject must be eligible prior to assigning treatment to/randomizing the subject.* From the left navigation menu select Assign Treatment

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

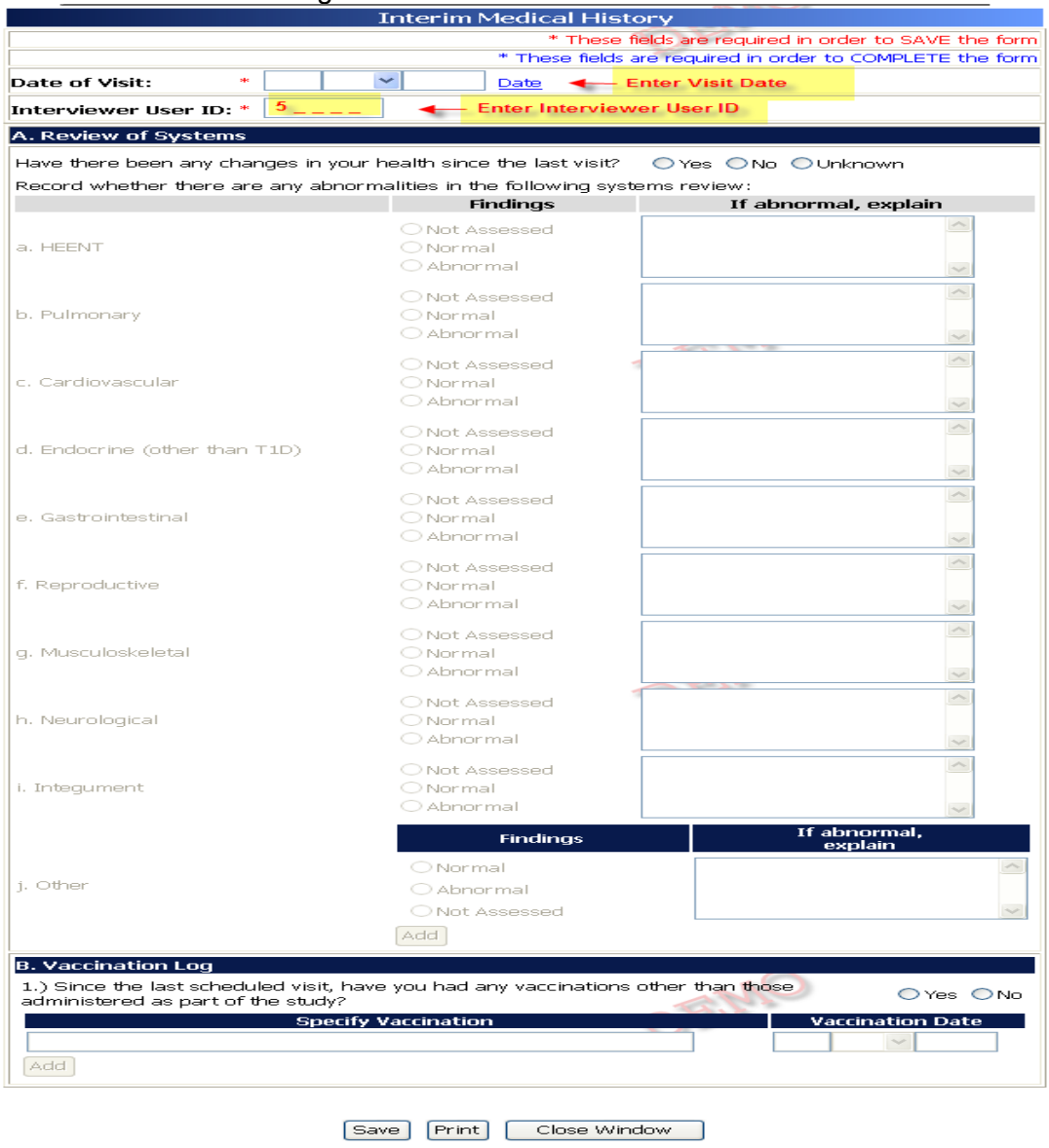
Step 1. Procedure to enter data for Interim Medical History: Be sure the Source Document is completed prior to completing this specimen collection form.

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

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

Step 4. Complete the following sections:

i. Review of Systems
ii. Vaccination Log

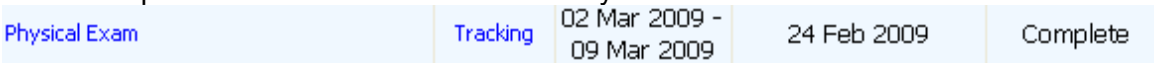


Step 5. After entering data, please reference section 9.1.4 Save and Close e-CRF

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



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.*

ii. Section B. Neurological Assessment

- *Collect information if the participant had any neurological assessments done and if there were any abnormalities.*

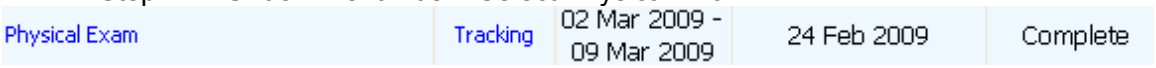
iii. Section C. Pregnancy Monitoring

- *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.*

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 Physical Exam



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. 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

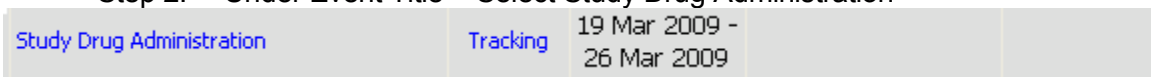
Step 3. When the form displays, enter Date of Visit and your Interview User ID

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

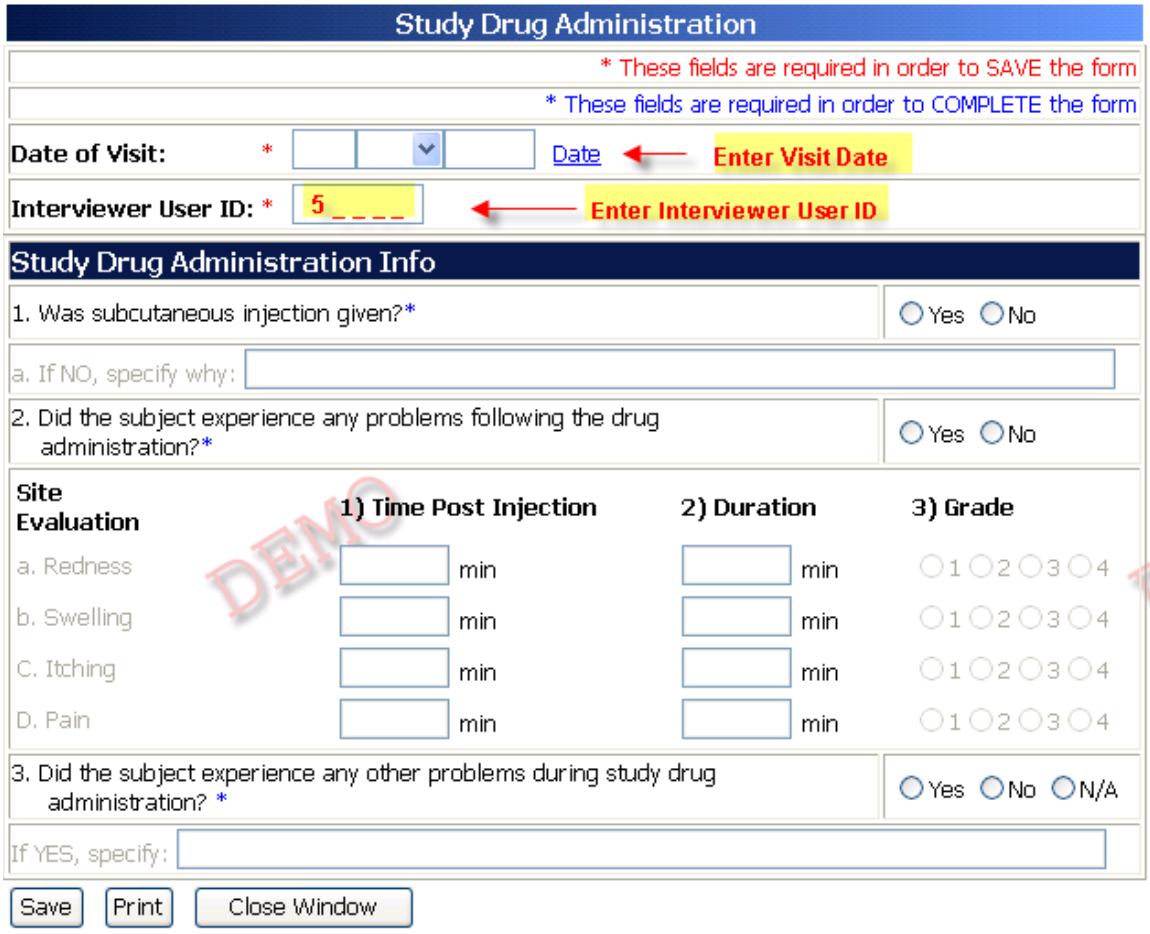
Step 2. Under Event Title - Select Study Drug Administration



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.*



9.4.8 Specimen Collection: Cellular Immunoblot

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

Step 2. Under Event Title - Specimen Collection Cellular Immunoblot

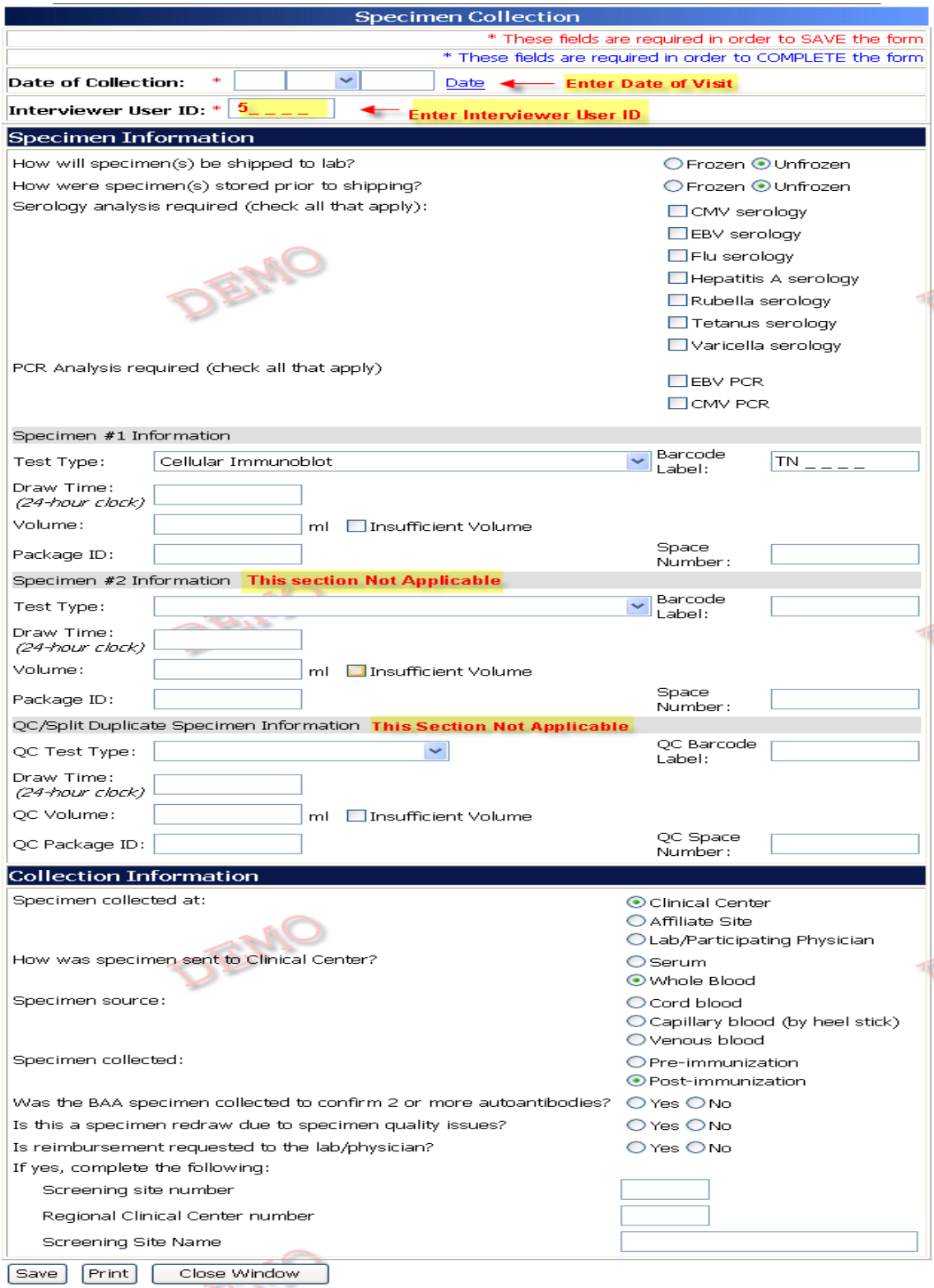
Step 3. Once the form displays, enter Date of Visit and Interview User ID

Step 4. Complete Specimen Information

i. Complete how specimen will be shipped to lab
ii. Select Test Type: Cellular Immunoblot
iii. 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)

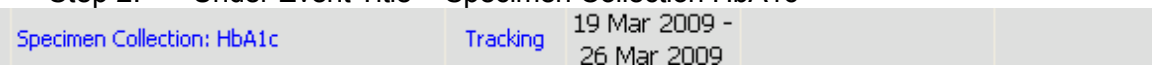
Step 5. Complete Collection Information



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



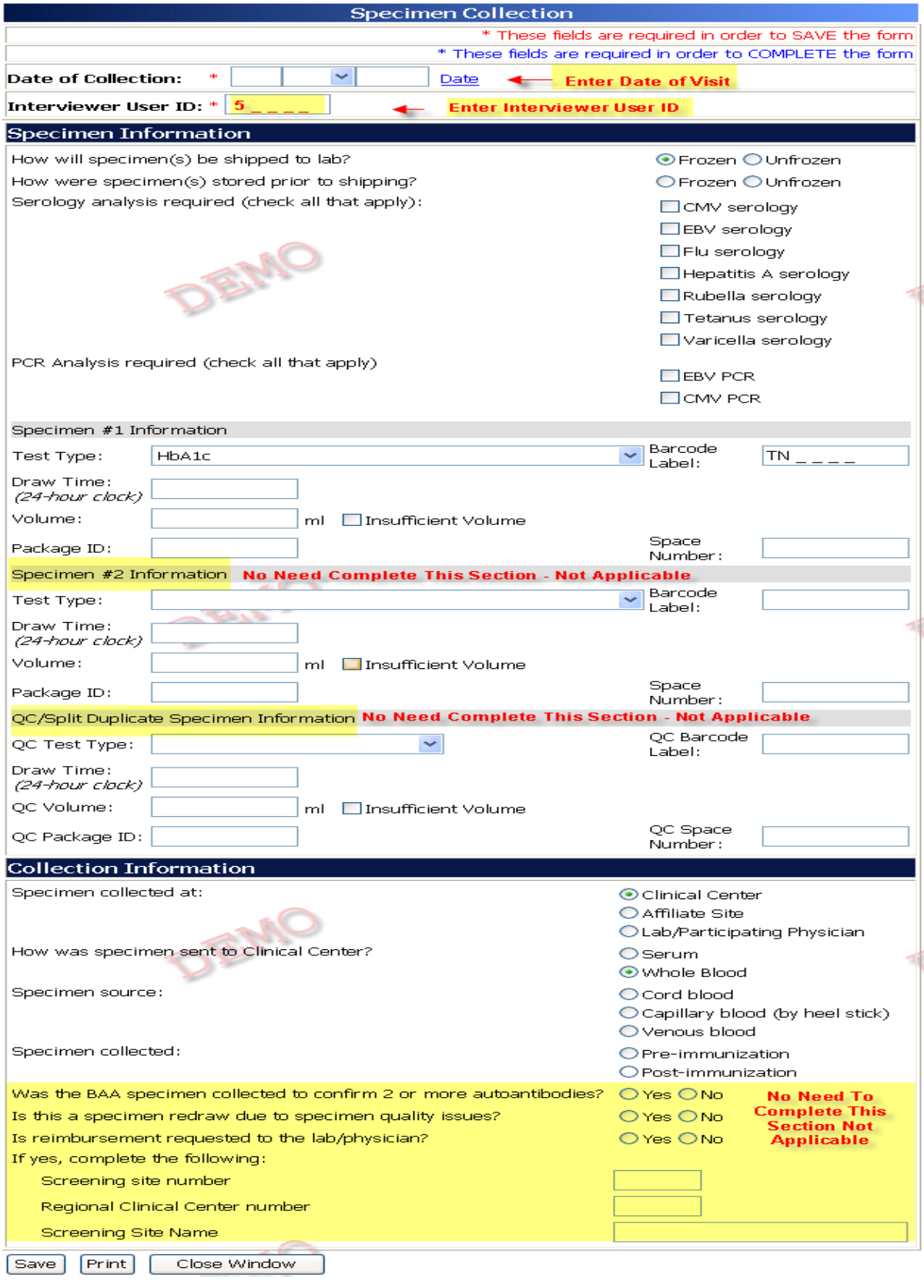
Step 3. Once the form displays, enter Date of Visit and Interview User ID

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)

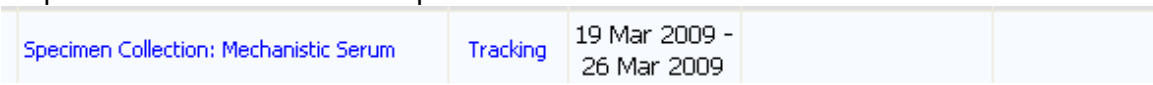
Step 5. Complete Collection Information



9.4.10 Specimen Collection: Mechanistic Serum

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

Step 2. Under Event Title - Specimen Collection Mechanistic Serum



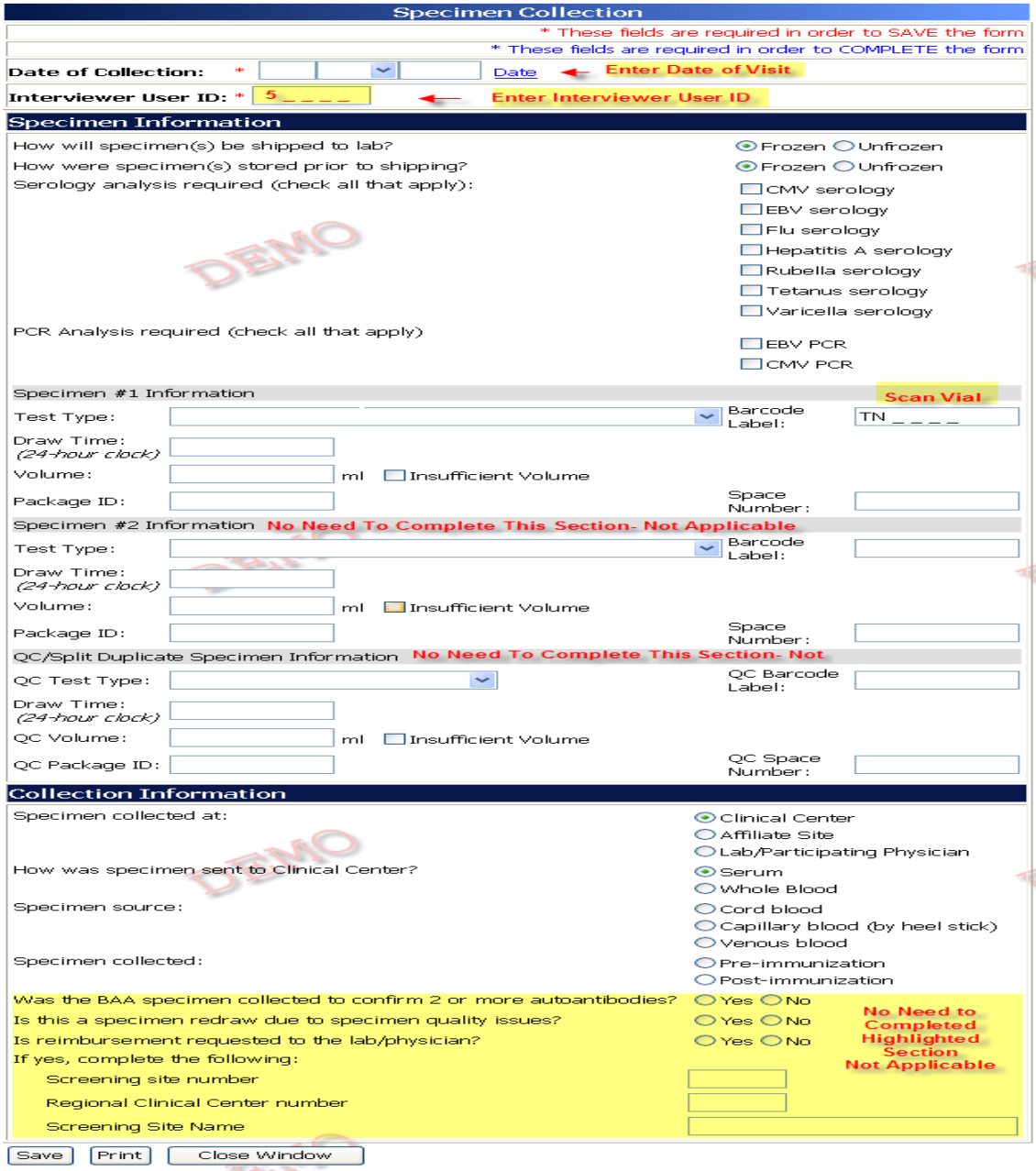
Step 3. Once the form displays, enter Date of Visit and Interview User ID

Step 4. Complete Specimen Information

i. Complete how specimen will be shipped to lab
ii. Select Test Type: Mechanistic Autoantibodies *(Note: will be updated to reflect Mechanistic Sample)*
iii. 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



Once Baseline Visit is completed the rest of the visit windows will open for treatment and follow up visits:

9.5 Visits 1-10: Follow-Up Visits

All other study visits (visits 1-10) 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

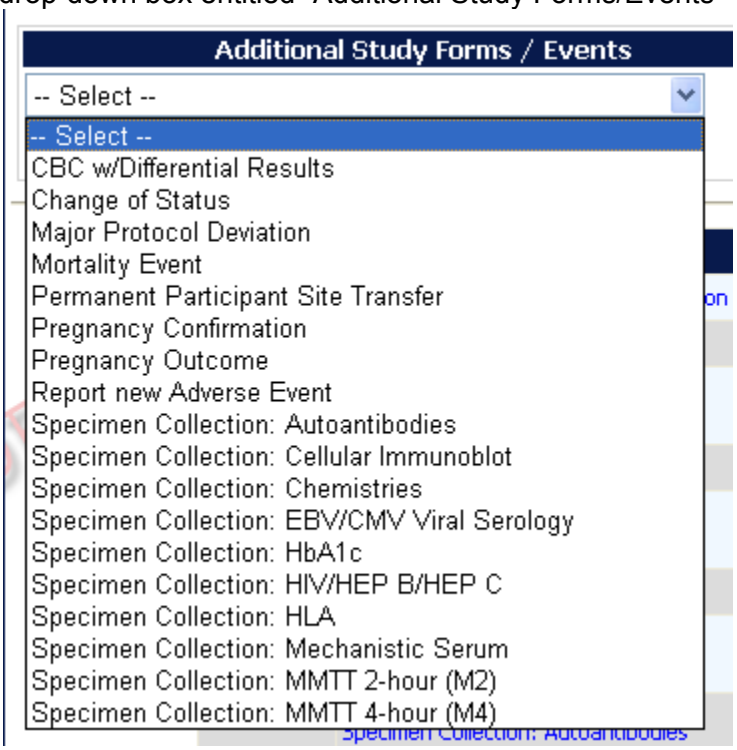
Definition: PRN – "When necessary"

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. Major Protocol Deviation: a protocol deviation occurs (subject is dosed from wrong kit, assessments or assays are not done, etc)
3. Mortality Event: a subject dies
4. Permanent Participant Site Transfer: a subject moves from one study site to another
5. Pregnancy Confirmation: a participant is determined to be pregnant
6. Pregnancy Outcome: the outcome of the pregnancy at pregnancy end point (meaning, the subject gives birth, miscarries, etc)
7. Report New Adverse Event: a subject experiences a reportable adverse event
8. 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

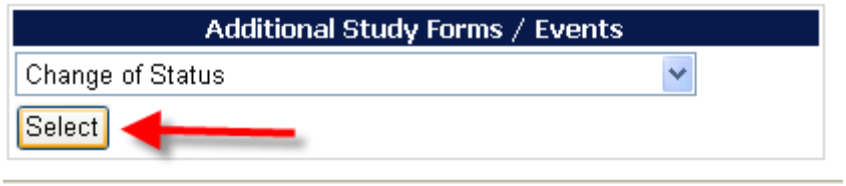
9.6.2 Open a New Additional Study Form/Event (PRN Form)

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



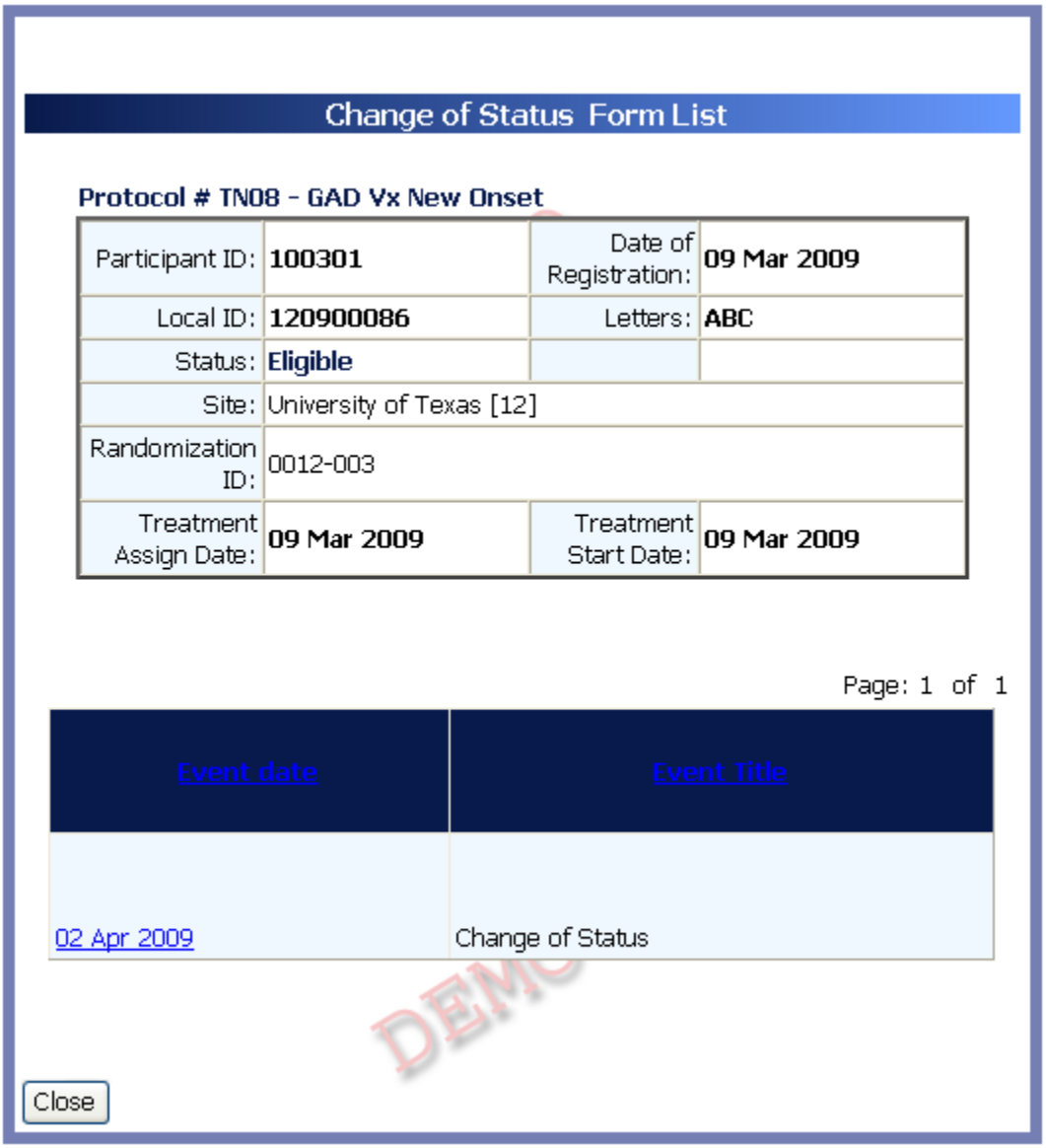
Step 4. A new window will open with the selected form.

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.

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

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.

10.3 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.

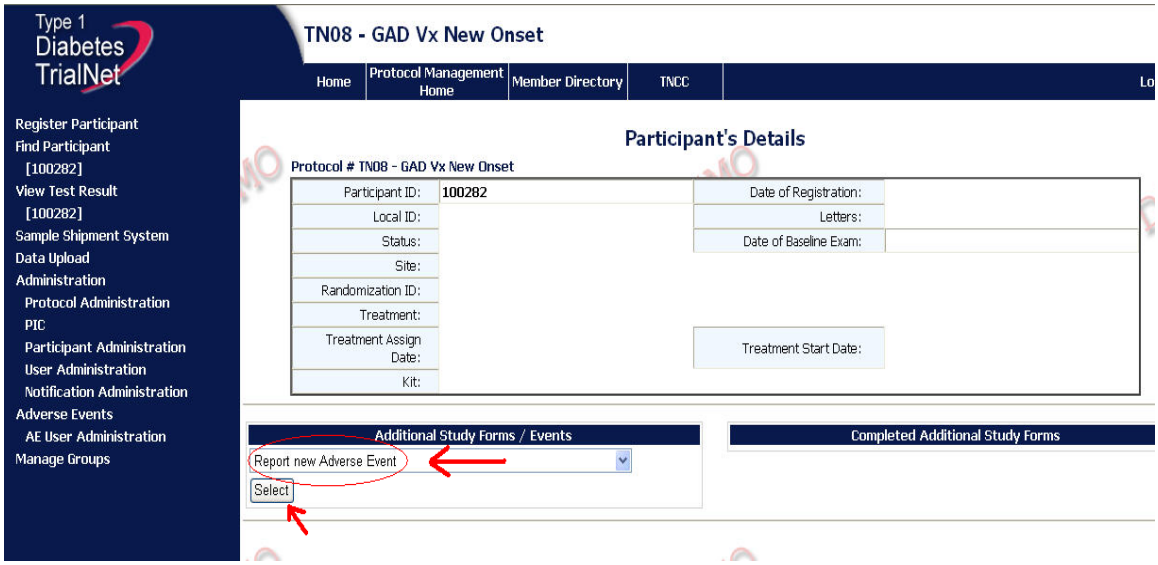
Step 3. From the left navigation menu on the main page, Select TN08 GAD Vx New Onset.

Step 4. A new window opens to the TN08 GAD 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.

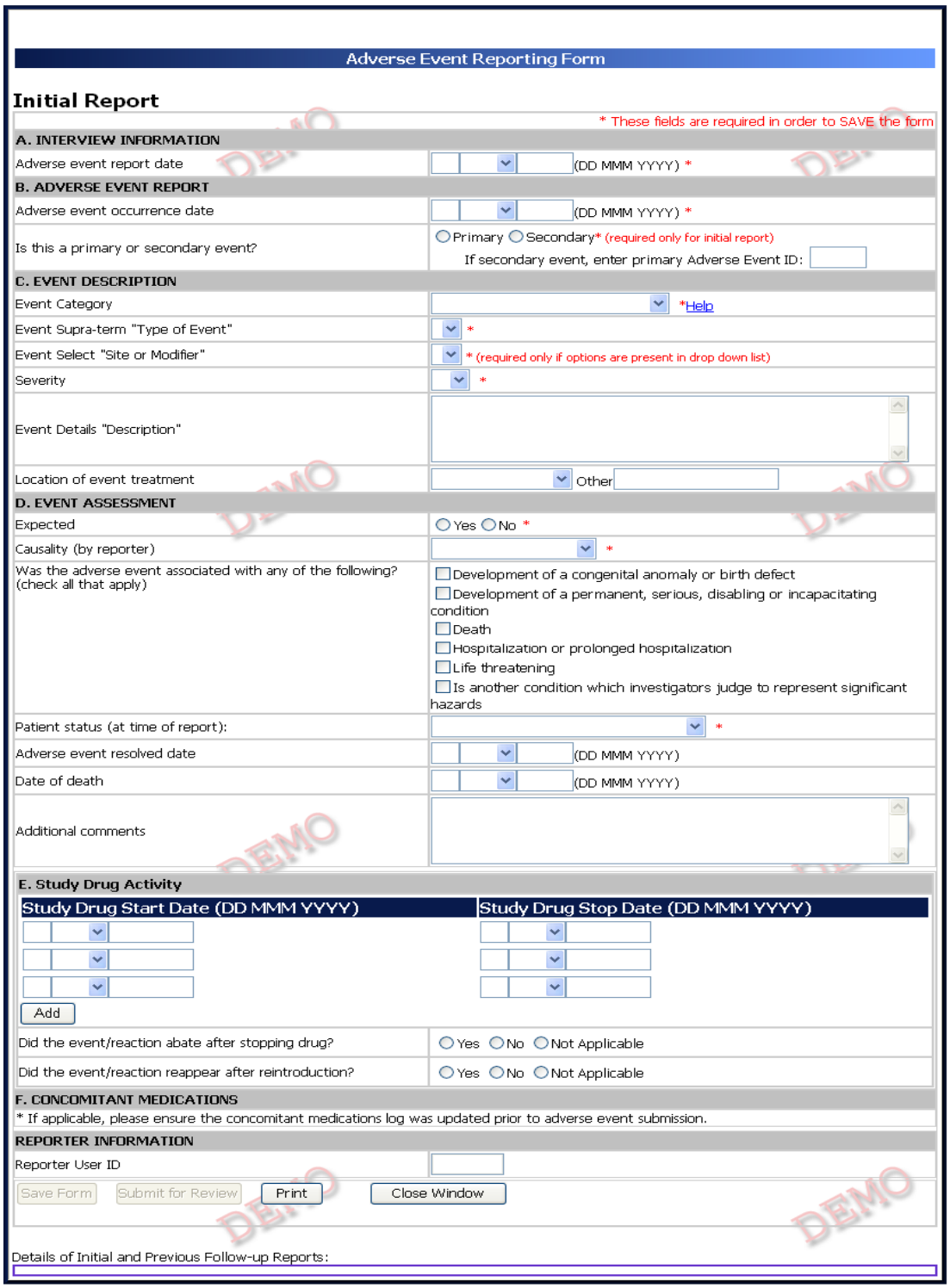
Step 6. The Participant's Details page is now displayed.

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

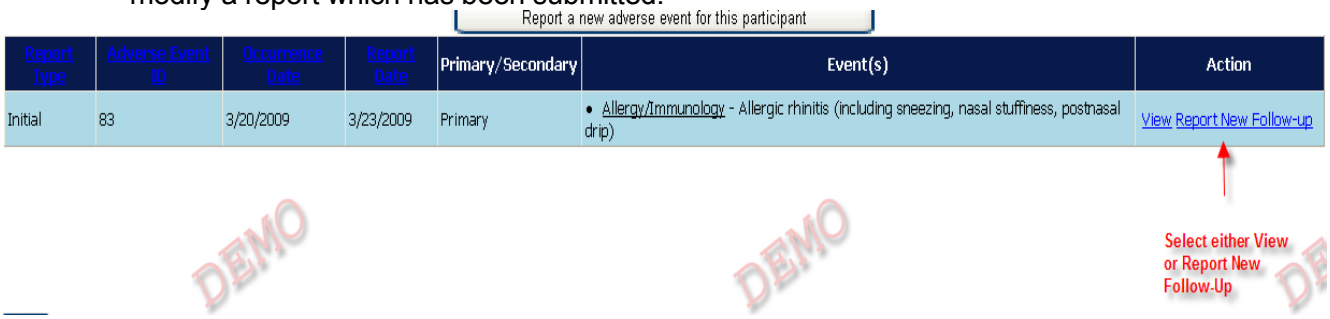
Save Form | Submit for Review | Print | Close Window

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.

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 TN08 – FAQ Folder

This folder contains the latest FAQ document for the study. Within you will find helpful resources for answering questions from the IRB as well as general study questions.

11.2 TN08 – Forms: Checklists and Source Documents Folder

This folder contains the latest study visit checklists and sample source documents (which should be used at each visit)

11.3 TN08 – Forms: Pharmacy Folder

This folder contains the latest versions of the pharmacy forms- used to order drug, return drug, and for study drug inventory

11.4 TN08 – GAD Certification Quiz Folder

This folder contains the latest the GAD Certification Quiz which should be used by sites, completed, and sent to the chairman's office for review prior to initiating the study

11.5 TN08 – Protocol Documents Folder

This folder contains the latest protocol documents, including:

1. Final Protocol
2. Consent/Assent Documents
3. Volunteer Understanding Survey
4. Study Handbook
5. Reimbursement Schedule
6. Memos and Letters for submission to site IRB
7. The blood volume table
8. FOLDER: Manual of Operations (11.5.1)

11.5.1 Manual of Operations

This folder contains the latest Manual of Operations as well as the Pharmacy Manual

11.6 TN08 – Reports Folder

This folder contains study reports.

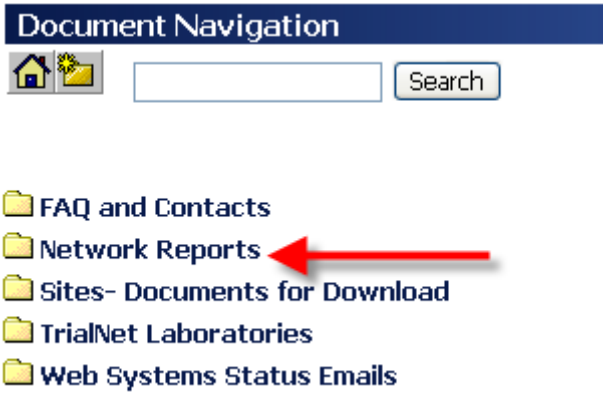
11.6.1 Reports Currently Available

Path	Report Title	Report Description	Updated
-Network Wide Reports-			
Main site → Network Reports → General Reports	GEN.I.01.Accrual Report By Protocol.rtf	Displays for all sites, all protocols- accrual total over time.	Monthly
Main site → Network Reports → Clinical Center → General Reports	GEN.II.01.Accrual Report By Protocol.rtf	Displays for a clinical center, all protocols at all affiliate sites (including the clinical center)- accrual total over time.	Monthly
Main site → Network Reports → Clinical Center → Site Folder	GEN.III.01.Accrual Report By Protocol.rtf	Displays for a specific site, all protocols- accrual total over time.	Monthly
-Study Specific Reports, General-			
Protocol Management Area → TN## - Reports → General Reports	TN##.I.01.Accrual Report By Clinical Center.rtf	Displays for a specific protocol, by clinical center- accrual totals for all sites	Monthly
	TN##.I.02.Actual.v.Expected Accrual - Graph.rtf	Displays for a specific protocol, for all sites- graph of actual verses expected accrual	Monthly
	TN##.I.03.IRB Summary - Ethnicity, Race and Gender Report.rtf	Displays for a specific protocol, for all sites- IRB summary of ethnicity, race and gender	Monthly
	TN##.I.04.IRB Summary - AE Report.rtf	Displays for a specific protocol, for all sites- IRB summary of all AE's	Monthly
Protocol Management Area → TN## - Reports → Clinical Center → General Reports	TN##.II.01.Accrual Report By Institution (CC#).rtf	Displays for a specific protocol, for a clinical center and its affiliates- accrual totals	Monthly
	TN##.II.02.IRB Summary - Ethnicity, Race and Gender Report (CC#).rtf	Displays for a specific protocol, for a clinical center and its affiliates- IRB summary of ethnicity, race and gender	Monthly
	TN##.II.03.IRB Summary - AE Report (CC#).rtf	Displays for a specific protocol, for a clinical center and its affiliates- IRB summary of all AE's	Monthly
Protocol Management Area → TN## - Reports → Clinical Center → Site Folder	TN##.III.01.Accrual Report (CC#_Site#).rtf	Displays for a specific protocol, for a specific site- accrual totals	Monthly
	TN##.III.02.IRB Summary - Ethnicity, Race and Gender Report (CC#_Site#).rtf	Displays for a specific protocol, for a specific site- IRB summary of ethnicity, race and gender	Monthly
	TN##.III.03.IRB Summary - AE Report (CC#_Site#).rtf	Displays for a specific protocol, for a specific site- IRB summary of all AE's at that site	Monthly
	TN##.III.04.Study Center Scheduling Calendar (CC#_Site#).rtf	Displays for a specific protocol, for a specific site- a calendar of target dates for subjects' visits	Monthly
-Study Specific Reports, Requested/Special-			
<u>TN08 GAD New Onset</u>			
TN 01Protocol Management Area → TN01 - Reports →	None yet identified	NA	NA

General Reports			
Protocol Management Area → TN01 - Reports → Clinical Center → General Reports	None yet identified	NA	NA
Protocol Management Area → TN01 - Reports → Clinical Center → Site Folder	None yet identified	NA	NA

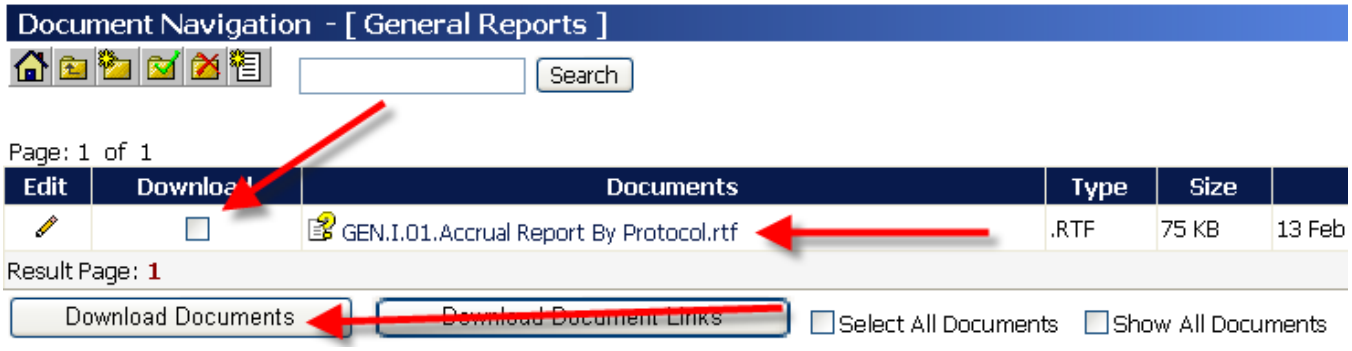
11.6.2 Network Wide Reports - All Sites, All Protocols

Step 1. From the main page, navigate the folder “Network Reports” under the document navigation area



Step 2. For reports that reflect network-wide totals, but are not specific to any particular site or protocol- select the folder “General Reports”

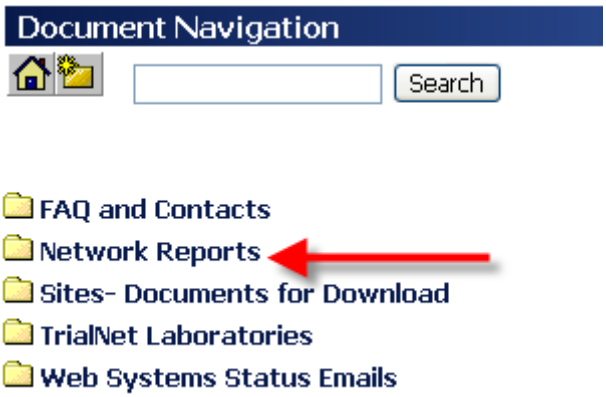
Step 3. Once there, you can click a report title to download a single report or you can select multiple reports to download by selecting the box under the column “Download” and clicking the button “Download Documents.” This will download multiple documents to your computer as a zip file.



11.6.3 Network Wide Reports - Reports by Site, All Protocols

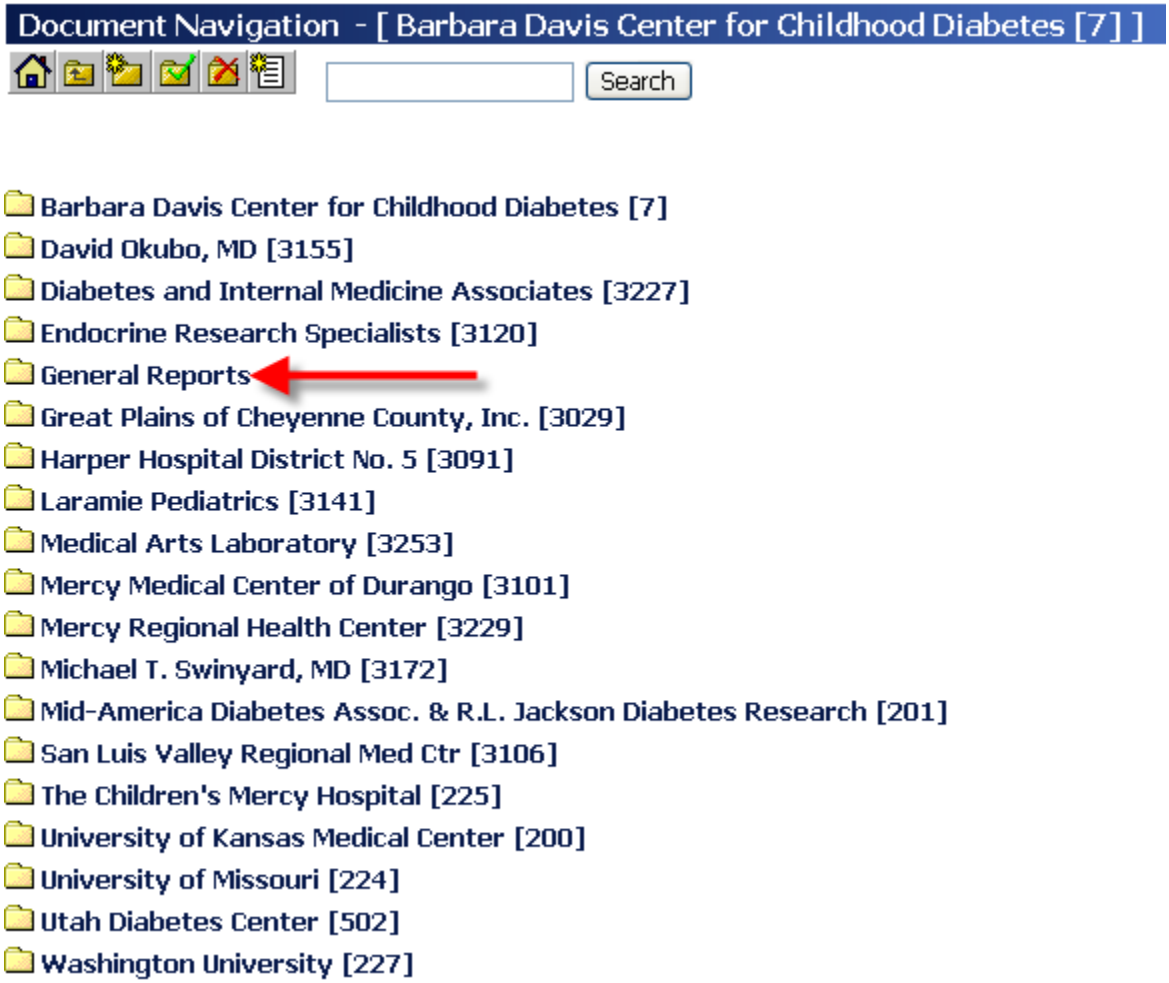
Reports by Site, Clinical Center Totals- All Protocols

Step 1. From the main page, navigate the folder “Network Reports” under the document navigation area



Step 2. For reports that reflect clinical center-wide totals, but are not specific to any particular protocol- select the folder with the name of the Clinical Center.

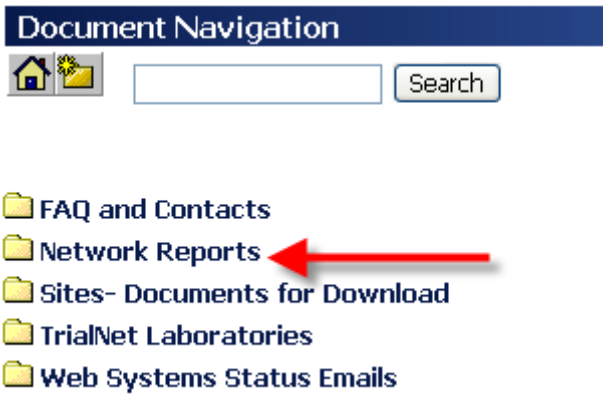
Step 3. Once inside the selected clinical center, select the folder entitled “General Reports”



Step 4. Once there, you can click a report title to download a single report or you can select multiple reports to download by selecting the box under the column “Download” and clicking the button “Download Documents.” This will download multiple documents to your computer as a zip file.

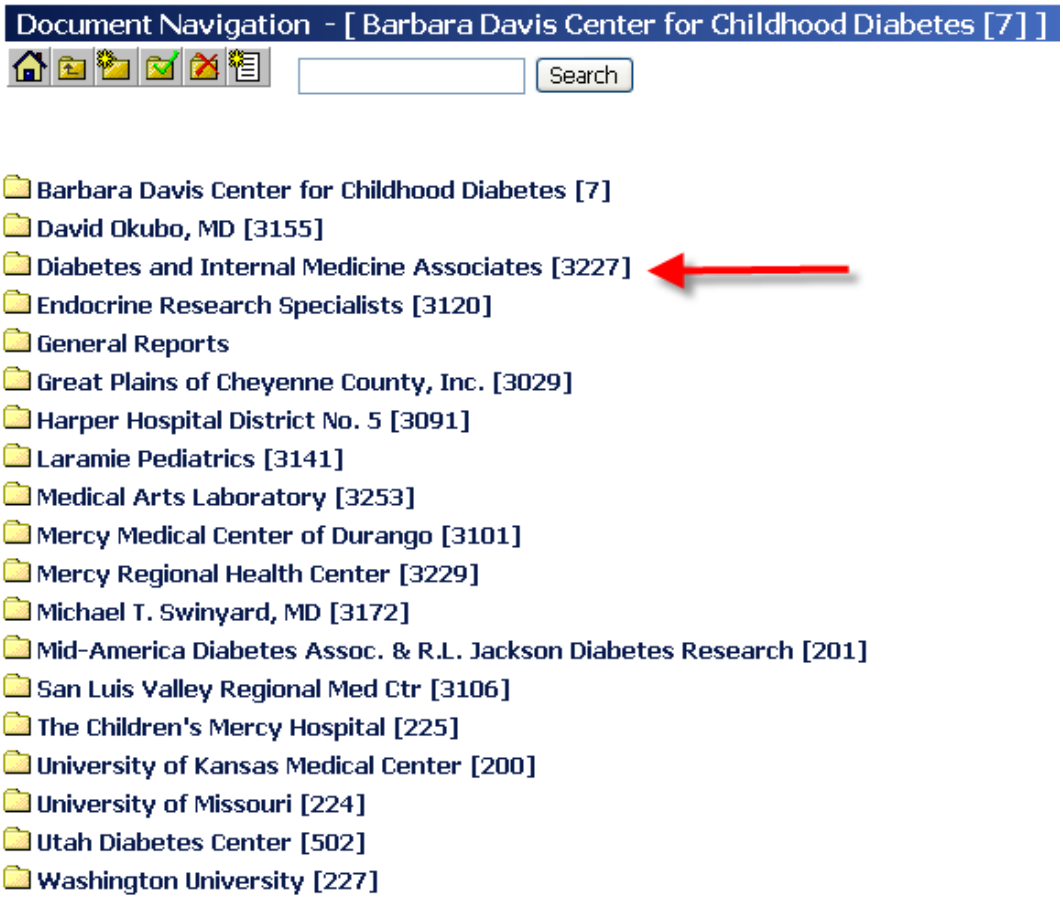
Reports by Site, Specific Site- All Protocols

Step 1. From the main page, navigate the folder “Network Reports” under the document navigation area



Step 2. For reports that reflect totals for a specific site, but are not specific to any particular protocol- select the folder with the name of the specific site's Clinical Center.

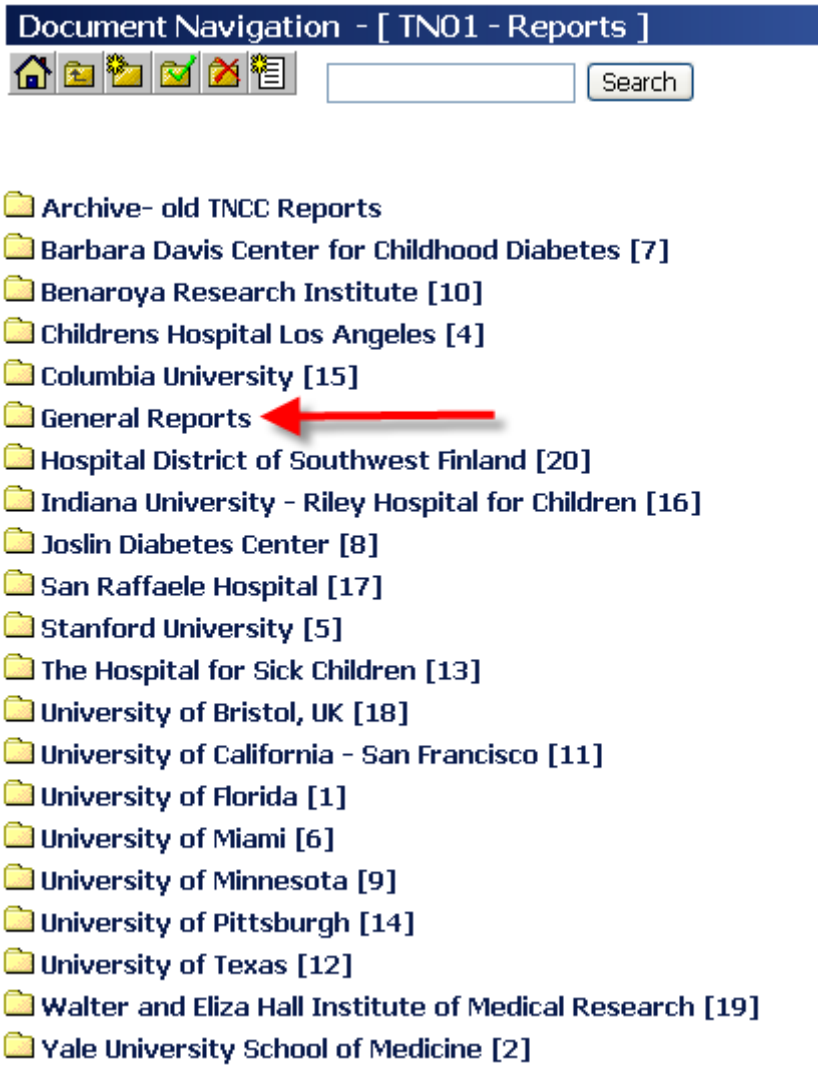
Step 3. Once inside the selected clinical center, select the folder entitled with the name of the site for which you wish to view reports.



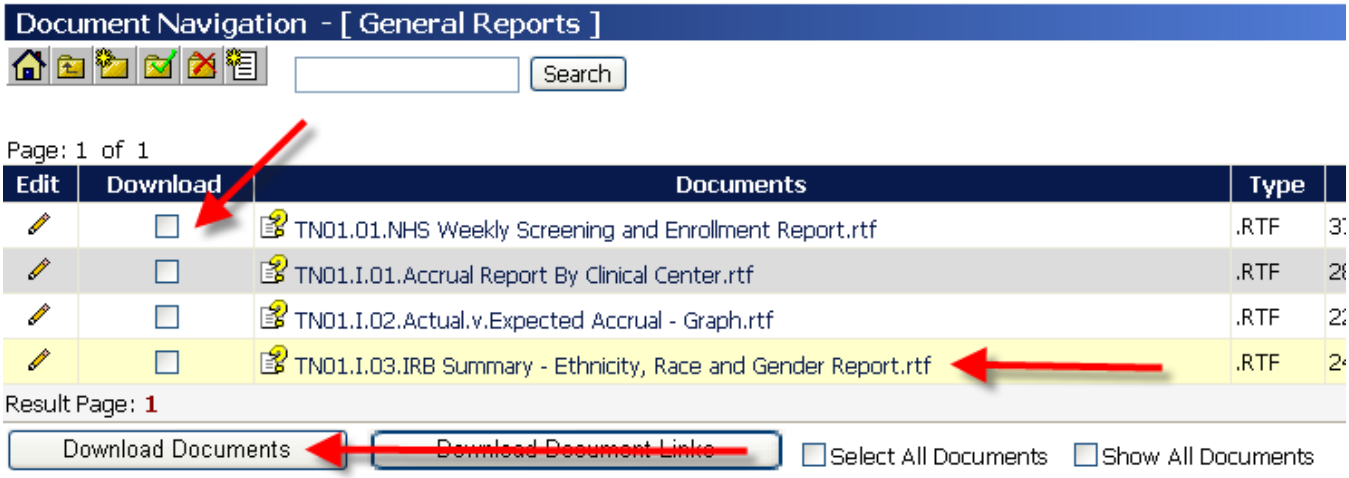
Step 4. Once there, you can click a report title to download a single report or you can select multiple reports to download by selecting the box under the column “Download” and clicking the button “Download Documents.” This will download multiple documents to your computer as a zip file.

11.6.4 Study Reports – All Sites

Step 1. For reports that are study-wide specific, but not specific to any particular site- select the folder “General Reports”



Step 2. Once there, you can click a report title to download a single report or you can select multiple reports to download by selecting the box under the column “Download” and clicking the button “Download Documents.” This will download multiple documents to your computer as a zip file.

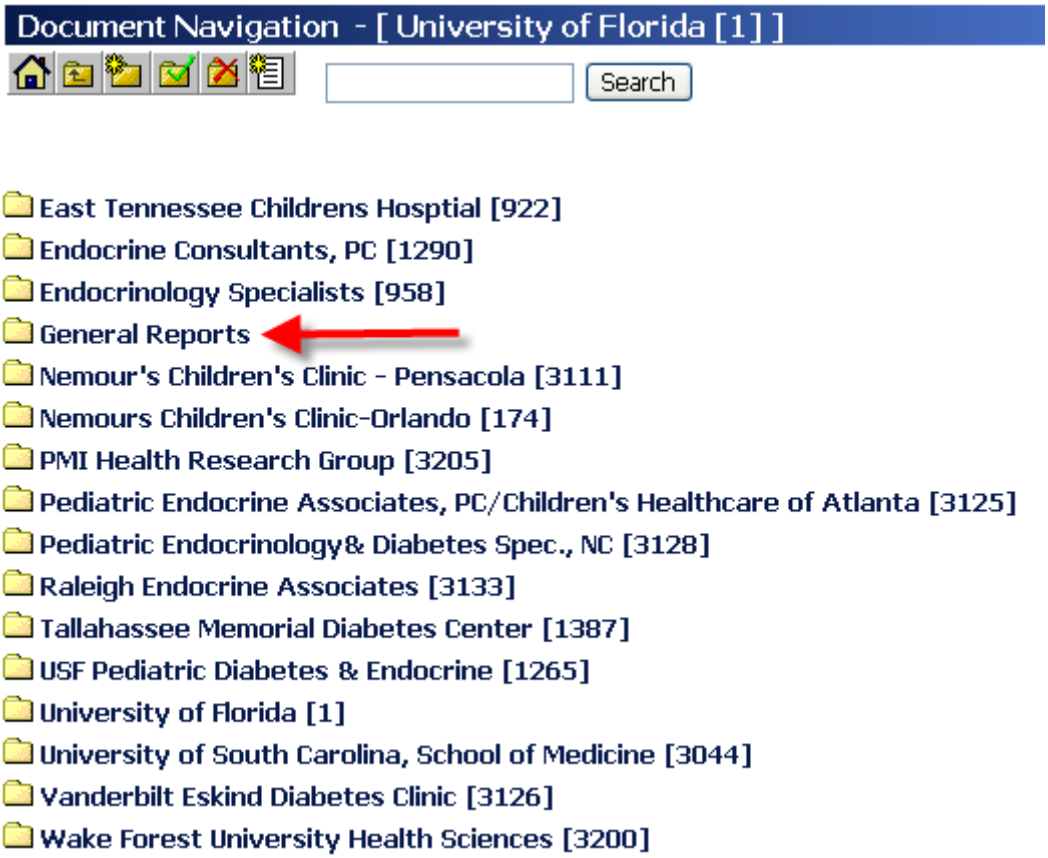

Document Navigation - [General Reports]
Search
Page: 1 of 1
Edit
Download
Documents
Type
TN01.01.NHS Weekly Screening and Enrollment Report.rtf
.RTF
TN01.I.01.Accrual Report By Clinical Center.rtf
.RTF
TN01.I.02.Actual.v.Expected Accrual - Graph.rtf
.RTF
TN01.I.03.IRB Summary - Ethnicity, Race and Gender Report.rtf
.RTF
Result Page: 1
Download Documents
Download Document Links
Select All Documents
Show All Documents

11.6.5 Study Reports – Clinical Center Level

Clinical center level reports will display data for a specific study all sites under the clinical center (including the clinical center)

Step 1. For reports that are Clinical Center specific for a study- select the folder with the name of the Clinical Center.

Step 2. Once inside the selected clinical center, select the folder entitled “General Reports”



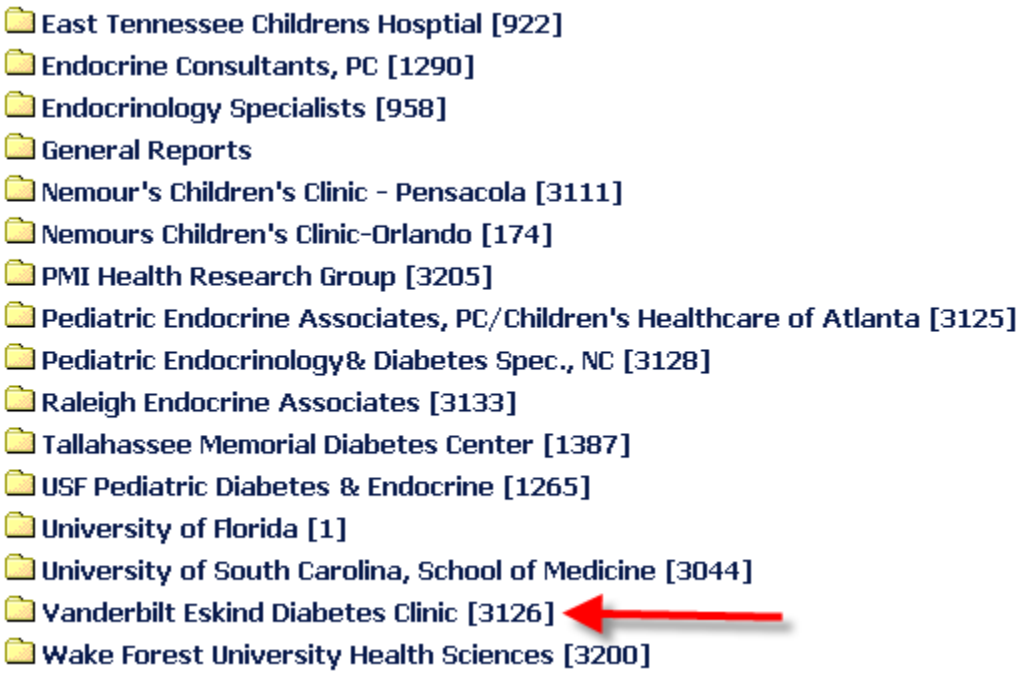
Step 3. Once there, you can click a report title to download a single report or you can select multiple reports to download by selecting the box under the column “Download” and clicking the button “Download Documents.” This will download multiple documents to your computer as a zip file.

11.6.6 Study Reports – Specific Site Level

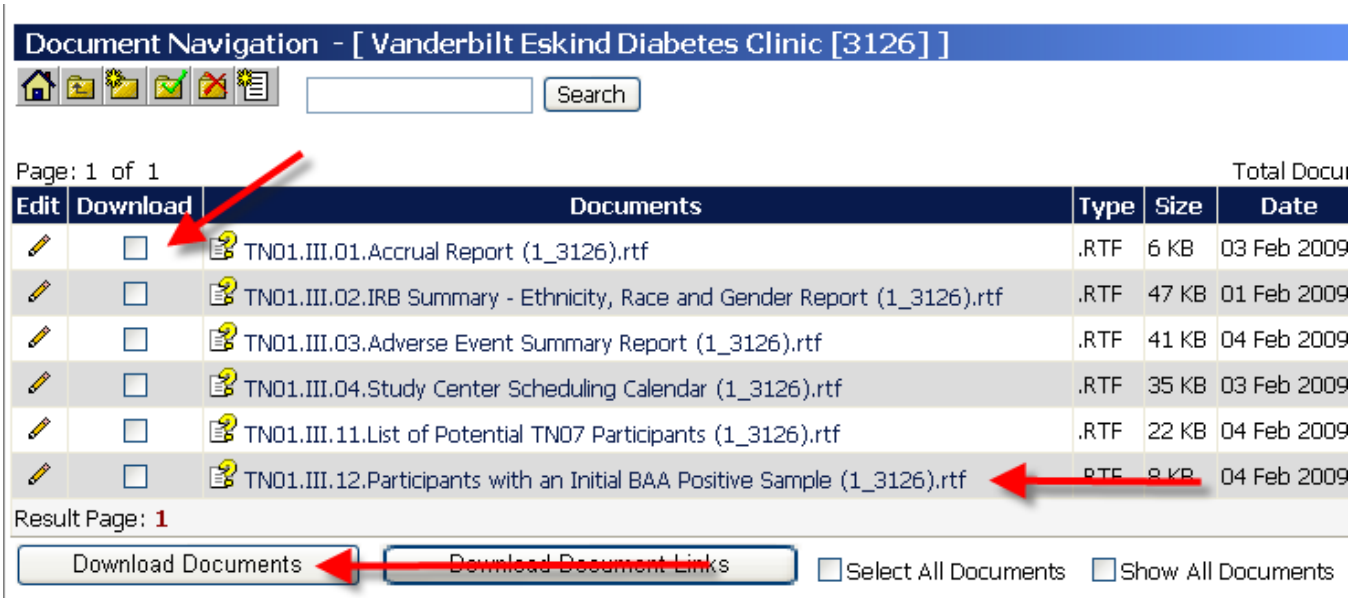
Site level reports will display data for a specific study only for 1-specific site

Step 1. For reports that are single Site (or Affiliate Site) specific for a study- select the folder with the name of the Clinical Center (or responsible Clinical Center for an affiliate site).

Step 2. Once inside the selected clinical center, select the folder entitled with the name of the site for which you wish to view reports



Step 3. Once there, you can click a report title to download a single report or you can select multiple reports to download by selecting the box under the column “Download” and clicking the button “Download Documents.” This will download multiple documents to your computer as a zip file.



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.

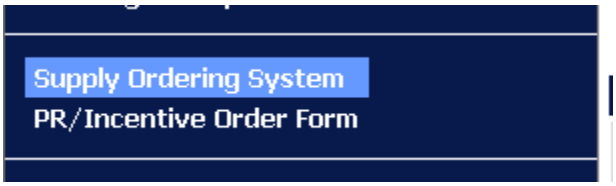
12.1.1 ITN

Please refer to the ITN manual for ordering procedures

12.1.2 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.

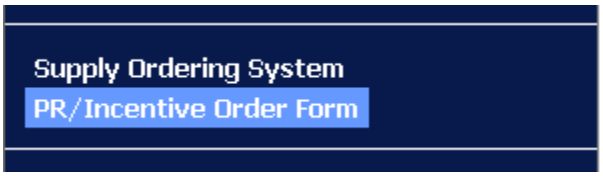
Step 6. Submit your order.

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 - MMG

12.4 Blood Glucose Monitors

Contact the TNCC CRA for the study to order Blood Glucose Monitors