Manual of Operations

NIP Diabetes Pilot Trial
TN-06

Draft Version

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CHAPTER 1 NIP DIABETES PILOT TRIAL

1. Overview

The primary objective of the NIP Diabetes Pilot is to assess the feasibility of implementing a full-scale study. Five objectives will be assessed for this pilot trial:

- Recruitment: Nine clinics will each enroll an average of ten subjects in one year.
- Treatment compliance: At least 90% of families will continue to take capsules/formula as instructed.
- Visit compliance: At least 95% of families will continue to attend follow-up visits to end of the study.
- At least a 20% higher level of plasma and/or red blood cell membrane phospholipid DHA can be achieved in the treatment group in comparison with the placebo group.
- At least a 20% lower level of the major inflammatory cytokine IL-beta can be achieved in the plasma of the treatment group in comparison with the placebo group.

The NIP Diabetes Pilot Trial is a 2-arm randomized, double blind, controlled comparison of omega-3 fatty acid (DHA) supplementation versus control. This pilot trial will develop information which can be used in a larger study should this trial prove to be feasible. In a full-scale study, the treatment's effect on the prevention of islet cell autoantibody development will be studied.

The feasibility study will include 90 infants, 2 arms with 45 infants in each arm which will be enrolled prior to 6 months of age (approximately half enrolled when the mother is in the third trimester of pregnancy and the other half within 6 months after birth). The infants enrolled in the study will be those who meet the eligibility criteria and whose parent(s) provided written consent. Eligible pregnant mothers and infants will be randomized into either the group receiving the DHA supplement or into the control group.

CHAPTER 2 PARTICIPATING SITES

Clinical Centers and Affiliates

Clinical sites and affiliate sites are designated sites with responsibility for the screening of potential participants, enrollment of participants, and conduct of the protocols of the TrialNet Type 1 Diabetes Network. Each clinical site and affiliate site will have a Principal Investigator, a full time Site Coordinator with other investigators, and ancillary personnel as needed. The Principal Investigator will work with the TrialNet Coordinating Center, Protocol Chairman, and NIH Staff assigned to this project to conduct the study in accordance with the Protocol, the Manual of Operations, and Good Clinical Practices.

There are 9 participating sites throughout the United States:

California Children's Hospital Los Angeles Los Angeles, CA Children's Hospital of Orange County Orange, CA University of California, San Francisco San Francisco, CA	**Indiana** Riley Hospital for Children **Indiana University - Indianapolis, IN** **Iowa** University of Iowa Health Care Iowa City, IA **Massachusetts** Joslin Diabetes Center Children's Hospital Boston Boston, MA
Minnesota University of Minnesota Minneapolis, MN	**Missouri** The Children's Mercy Hospital Kansas City, MO
Utah University of Utah Utah Diabetes Center Salt Lake City, Utah	

CHAPTER 3 INFORMED CONSENT PROCESS

1. Informed Consent Process

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.

In the NIP Diabetes Pilot, the participant is an unborn or very young child. Therefore, any mention of "participant" within the realm of consent, signatures, or discussion about the study will refer to the parent(s), guardian, or other family members who may be involved. Fathers, guardians, or other family members may enroll their infant through Entry B if the mother is deceased or unable to be contacted. They will follow the Entry B non-nursing path and omit any mother blood draws that are otherwise required.

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 for the NIP Diabetes Pilot Trial 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.

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 after a thorough discussion of the study. It is required that an attempt be made to obtain the signatures of both parents. In the case of a one parent family where the attempt to contact the second parent is unsuccessful, one signature will be generally acceptable, however each site's IRB or state laws will influence the requirements for each site. TNCC is available for assistance if the guidelines for a specific situation remain unclear. 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.

The participant needs to **initial the bottom of each page** of the consent and **sign/date the last page.** The signature, the current date, and the printed name of the participant are all required. Next, the person obtaining the consent (the person who has explained the study to the participant), must sign the form, provide the current date and print his/her name. Please ensure that the printed areas are completed legibly.

If a mother is entered prenatally, re-consenting must occur after the birth of the child using the Infant Enrollment Consent.

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.

2. Participant Handbook

As part of the informed consent, participants should be given a copy of the Participant Handbook before signing the Consent. Participant should read it and the study coordinator should use it as a tool to explain the study to the participant.

3. Volunteer Understanding Survey

As part of the informed consent process, the participant will be required to complete a short, written *Volunteer Understanding Survey* that is designed to ensure the participant understands the study, as well as what is being asked of him or her. The survey should be given to the participant following a description of the study and before the *Informed Consent Form* has been signed. Study personnel will review the completed survey with the participant, taking special care to review any questions the participant answered incorrectly and to answer any questions about the study. The purpose of the survey is to enhance the informed consent process and to reinforce the main points of the study. There is no score for the Volunteer Understanding Survey. There are two different Surveys depending on when the participant will be enrolling the study:

- Entry A: Volunteer Survey for Enrollment During Pregnancy
- Entry B: Volunteer Survey for Infant Enrollment

Both surveys and answer keys for both are available on the NIP Diabetes Pilot section of the TrialNet website and in Appendix D.

4. Stored Samples

In addition to the standard procedures and tests associated with the study, participants will be asked for permission to store their remaining blood samples including genetic samples for future studies to learn more about factors associated with risk for the development of type 1 diabetes. The participant must indicate their choice on the Informed Consent Forms and initial in the appropriate area.

- Participants are **not** required to provide consent for stored samples in order to participate in the study.

- Participants also have the right to withdraw their consent to store samples at any time and to have their stored samples destroyed to the extent possible. See Appendix B for instructions for Requesting the Destruction of Samples.

Samples may be destroyed during the course of TrialNet; however they may no longer be destroyed after TrialNet is complete since all information will be stripped from the sample. If a participant indicates that they would like to have samples stored but then retracts their statement at a later date, contact TNCC for guidance on how to proceed.

5. Continuing Consent

If there is a revision to the original IRB Approved Informed Consent signed by the participant, he/she must be re-consented with the current IRB Approved Informed Consent.

CHAPTER 4 SITE CERTIFICATION AND REQUIREMENTS

Participating clinical sites must fulfill specific requirements prior to the start of any protocol activity. When a site has met all requirements to start the study, a written notice of **"Site Certification"** will be issued by the TrialNet Coordinating Center. Once authorized to start protocol enrollment, the site will have a continuing responsibility to update the TrialNet Coordinating Center of any changes, such as personnel changes. Reminders for annual renewals of documents will be sent to the Principal Investigators and Study Coordinators two months in advance of renewal dates.

1. Documents to be sent to TrialNet Coordinating Center:

The following items are collected and maintained at the TrialNet Coordinating Center (TNCC):

1. IRB approval for study (includes IRB letter of approval for protocol and stamped informed consents; additionally, a copy of the IRB approved Research Subject Authorization Form)
2. Annual renewal of IRB approvals
3. Executed Letter of Agreement (LOA) with The George Washington University (GWU)
4. Confidentiality Agreement completed by each Research Staff member
5. Duality of Interest Forms (DU1 and DU7) completed by each Research Staff member
6. Annual update to DU1 by completed DU2 or DU3
7. NIH Education on Human Subjects Protections or equivalent proof of training for each Research Staff member
8. Research staff names, mailing addresses, email addresses, office FAX/telephone numbers
9. Curriculum vitae for all professional personnel (physicians, site coordinators, study coordinators, nurses, etc.)
10. Completed and signed Financial Disclosure Form if applicable (Form FDA 3455)
11. Name and location of laboratory utilized for local laboratory assays, such as HbA1c and glucose and other facilities conducting tests, including a copy of the laboratory certificate
12. Normal value ranges for HbA1c and glucose (local laboratory)
13. Completed Eminent forms for study formula and study capsules to indicate the on-site location where study formula and study capsule shipments will be received

14. Provide TNCC with a pass-phrase for web randomization system. Refer to Chapter ___ for more information.
15. Protocol certification (Study Quiz)
16. Original University of Florida Confidentiality Agreement
17. Completed Site Initiation Checklist

2. Site Initiation Activity Checklist (Appendix C):

Research personnel at the site must complete the The Site Initiation Activities Checklist (it can be found in the TrialNet Website). This list will serve as documentation that the following items have been completed, among others:

- Availability of –20° C freezer for storage of frozen samples
- Local courier service for delivery of study substance to participant's home has been set up
- A plan for cord blood collection logistics has been finalized
- Review of current protocol, study procedures, Adverse Event Monitoring Plan, CTCAE v3, CTCAE Dictionary and Index, Intensity Grading Criteria for Vasovagal Events, and other study documents
- All staff members have read Section 6 of the protocol, Adverse Event Reporting and Safety Monitoring
- Complete the Randomization WebEx Training
- Complete a mock randomization
- Initial shipment of laboratory supplies has been received
- Receipt of NIP Diabetes Pilot Participant Binders and Barcodes
- Receipt of initial shipment of study capsules and study formula
- Review shipping procedures for TrialNet laboratory samples

3. IRB Approvals

A copy of IRB approved documents (letter of approval from site IRB, approved informed consent forms, and approved Research Subject Authorization Form) must be received and filed at the TNCC. The IRB documents must reflect the appropriate version number and date of the Protocol. To maintain requirements for continuing participation in TrialNet, the site must provide their annual renewal of IRB approval for the study.

4. Letter of Agreement (LOA)

The Letter of Agreement is a formal document that outlines the responsibilities of all parties for the conduct of the TrialNet studies. The LOA is addressed to the Principal Investigator at the institution and includes appendices of required forms that must be completed by the institution and its research staff that will be involved in TrialNet studies.

The LOA must be executed between The George Washington University (GWU) on behalf of the TNCC and Regional Clinical Centers and Affiliate Sites in order to establish the payment records for reimbursement of study related participant care costs. Only one LOA with GWU is required from the site. The LOA remains in effect throughout the duration of TrialNet.

5. Research Staff Requirements

Each TrialNet Research Staff member at the site is required to sign a TrialNet Confidentiality Agreement, Duality of Interest Form (DU1 and DU7), and complete the NIH Education on Human Subjects Protections or equivalent training. Annually, Research Staff will be requested to provide either a statement of no change (DU3) or conflict (DU2) to their original DU1. The TNCC will send reminders to research staff or Site Coordinators of impending renewal dates.

The site is expected to contact the TNCC on an ongoing basis of any changes or additions to Research Staff.

6. Clinical Staff Certification

Certification of staff is required for the NIP Diabetes Pilot Trial. At least one person (preferably and typically the lead Study Coordinator) at the site must be certified to satisfy requirements for Site Certification and initiate protocol enrollment activities.

Certification is an important step in ensuring that study procedures are performed consistently across all TrialNet sites. The NIP Diabetes Pilot Trial certification includes the following:

6.1. Study Quiz

This quiz is specific to the NIP Diabetes Pilot Trial and must be completed by staff at each participating site. The NIP Diabetes Pilot Study Quiz covers key points of the protocol (such as eligibility criteria and visit procedures), informed consent issues, the CRFs, blood draws and the specimen transmittal forms (STFs), operational decisions, sample handling, and shipping and study substance administration. There are 13 multiple choice and 8 true/false.

Before taking the quiz, the relevant study documents should be reviewed (see Table 1). Although staff may refer to these documents while taking the quiz, candidates should be familiar with the concepts covered in them.

Allow at least 30 minutes for the study quiz and 10 minutes for the Mock Randomization.

There will be a conference call with all participating Site Coordinators to review the study quiz. Site Coordinators must fax their completed study quiz two days prior to the call. The TNCC will notify the Site Coordinator of any incorrect responses. TNCC will go over incorrect responses and have a short question/answer session to review the study procedures. The Site Coordinator will then be responsible for giving and scoring the quiz and reviewing incorrect responses with their staff. In some cases, retesting may be necessary. The quiz can be found in the TrialNet Website.

6.2. Performance Demonstration: Mock Web Randomization

This will be completed by the Site Coordinator responsible for randomization at each participating site. After the TNCC has activated the Site Coordinator's pass phrase, they may log into the system. At first login, the Site Coordinator will be prompted to complete a mock randomization. After successful completion of the mock randomization, they may proceed to the live randomization. Please note that after completing the mock randomization, you must log out of the system and log back in, in order to have access to the live randomization system. If it says 'mock randomization' at the top of the page, you have not successfully refreshed the system. Refer to Chapter 9 for information on completing a mock randomization.

The Site Coordinator at each clinical site must be certified in all required components. In addition to the Site Coordinator, there are two general categories of staff that must be certified (see Table 1):

1) **Clinical Research Staff** - work directly with the Site Coordinator and are involved with the completion of case report forms (CRFs) and research participant files, consenting research participants, communicating with the TNCC, conducting participant visits, randomizing participants, and/or collecting and shipping specimens. These staff must complete all of the certification components listed above.

2) **Other Clinical Staff** - nurses and other staff at the GCRC or CRC who will collect specimens and/or prepare samples for shipment to the core laboratories. If blood collection is performed by a nurse at the CRC/GCRC we highly recommend that they be certified for this study. If this is not feasible, the site coordinator may write and sign a note indicating which site staff has been trained locally. If samples are found to be of low quality by the assay labs, then the CRC/GCRC staff will need to be certified before proceeding with future collections.

Table 1: NIP Pilot Trial Certification

COMPONENT	REFERENCES (Study documents)	WHO?		
		Site Coordinator	Clinical Research Staff	Other Clinical Staff
Study Quiz **(1)**	• Protocol • Informed Consent / Assent Forms • Case Report Forms • Specimen Transmittal Forms • Manual of Operations • Volunteer Survey • Participant Handbook	Required	Sometimes	Sometimes
Mock Randomization (**2**)	• Manual of Operations	Required	Sometimes	Not applicable

(1) Mandatory for Site Coordinator who will have daily operational management responsibilities. This component is required for anyone responsible for preparing specimens for shipment to labs.

(2) Required for one person at each site who will be randomizing participants.

7. Notification of Staff Certification

Site Coordinators certifying their staff should fill out the Notice of Staff Certification document and send it to TNCC along with the staff member's completed study quiz. This document can be found in the Site Certification folder located within the NIP Diabetes Pilot documents on the TrialNet website. The Coordinating Center tracks all completed certification components at each site and will notify individuals of their successful certification.

Reminder:

Any new Clinical Research Staff must also complete the following and submit to the TNCC:

- **TN Confidentiality Form**
- **TN Duality of Interest Form**
- **NIH Education Certification for Human Research Subjects Protection (or equivalent)**

CHAPTER 5 RECRUITMENT AND RETENTION

1. Overview

The NIP Pilot Trial consists of 9 clinical sites and affiliates throughout the United States.

Site Coordinators and Recruitment Coordinators (If applicable) should:

- generate general **awareness** about the study
- generate an **interest in participating** for those eligible,
- provide **education** on the goals of TrialNet.

Several tools for recruitment have been developed by TrialNet for use at the local level. Clinical sites should make use of each of the tools developed to recruit new participants. Always make sure to check with your IRB if approval is needed before using the Recruitment and Retention tools. Some of the tools developed for the study include:

- NIP Brochure
- NIP Poster
- NIP Pediatrician Recruitment letter
- NIP Obstetrician Recruitment letter
- NIP Pilot landscape summary
- NIP Pediatrician Retention Letter
- NIP Colleague Recruitment Letter

2. Participant Recruitment

Participants will be recruited through participating sites. Selection of participants for enrollment in the study will be done through a screening process that will involve two separate time points:

- during the third trimester of pregnancy or
- within the first 5 months after birth of the child

3. Recruiting Strategies

Each site will enroll approximately 10 participants over one year. It is expected that approximately one out of every 3 participants will be interested in and eligible for the Pilot Trial, therefore recruiting efforts should be well organized so each site can screen approximately 30 individuals. Suggestions for effective recruitment follow, however each site is encouraged to be creative with their own staff and resources.

Encourage the PI to be heavily engaged in recruiting efforts and in the trial itself. The PI has the opportunity to mention the study to potential participants at clinic visits and is likely to already have an established rapport with his/her patients.

Consider engaging others on staff as well. It may be ideal to have a number of professionals mention the study to participants at appropriate times. Consider educators, social workers, and nutritionists as part of the recruitment team.

Take some time to utilize other internal contacts that may have associations with your potential participants. This may include your obstetrics and gynecology department, family medicine, or colleagues in other departments.

Contact physicians in private practice or other outside clinics. Motivate them to be a part of this new research study and stress its importance. They may be willing to discuss the Trial with their patients and refer any interested individuals.

Consider public modes of communication such as the NIP Diabetes posters and brochures. Take the opportunity to give a brochure to anyone receiving insulin. You will be able to reach pregnant women, mothers, or those who have family members who might be interested in the study. Patients who call in for information about the Pilot Trial should be encouraged to inform friends or family members of the study, whether they themselves are eligible to

participate or not. Also, when individuals call in, ask them where they heard about the study so you can continue to use the most popular resources as advertising methods.

The media can also be a great way to spread the word and educate others about this research opportunity. Use TV, newspaper ads, mail newsletters and take advantage of expos if possible. You may also want to leave brochures at places such as diabetes supply stores, medical supply stores, or support group centers.

Start small and local to your site. For example, you may start with someone within your institution, an in-house or nearby hospital pharmacy, and 3 others of your choice. Once you have a start, you can branch out from there.

Understand that it may take time to establish these sources of referrals. Set aside several hours to talk with and educate your colleagues, physicians, and others. Build a rapport and keep communication open. Check back on a regular basis with those who are interested in helping with study recruitment. Let them know how their referrals are helping the study and how much you appreciate their time. Consider bringing them coffee or other inexpensive treats to thank them for their efforts.

Periodically evaluate all modes of advertising so you know which ones are effective and which ones are inefficient uses of time. Divert your resources accordingly to yield the best results. Recruitment is an ongoing effort so be sure to thank those that work with you and continually look for new ways to spread the word.

CHAPTER 6 ENTRY INTO THE NIP DIABETES PILOT TRIAL

1. Overview

Pregnant women in their third trimester and mothers of newborns less than 5 months of age will be identified and referred to participating TrialNet sites. The family will be asked if they would be interested in participating in a research project. Those indicating interest are referred to one of the Investigators or Study Coordinators for a description of the study. TrialNet research personnel authorized to present the study to families have attended an approved IRB course and are registered by the IRB.

Before any study specific procedures a copy of the Informed Consent and the Volunteer Understanding Survey should be given to the participant. Please refer to Chapter 3 for a complete description of the Informed Consent Process for the NIP Pilot Trial.

2. Scheduling Participant Visits

All visits should be scheduled Monday through Thursday, except for cord blood samples which may be shipped 7 days a week. Occasionally, a sample may be accepted by the lab on a Saturday, provided that the staff is notified by email at least one week prior to its arrival. The email notification should be sent to trialnet@pathology.ufl.edu as well as Sara Adams at TNCC sadams@bsc.gwu.edu. When scheduling a participant's visit, take into consideration holidays surrounding that visit**.**

No blood samples are to be shipped the day before a holiday.

3. Eligibility Criteria

Inclusion and exclusion criteria for the TrialNet NIP Pilot Trial are listed within the description of each respective entry point. The inclusion and exclusion criteria should be strictly adhered to as described in the NIP Pilot Protocol. Participants **must** meet all eligibility criteria prior to randomization, undergoing any baseline study procedures, or completing any study forms.

3.1. Eligibility Issues

The TrialNet Coordinating Center will be responsible for initially reviewing and adjudicating any instances where eligibility is unclear. Eligibility issues should be submitted by completing a study specific Eligibility and Deviation Review Form to the TrialNet Coordinating Center (Appendix D). The issue will be reviewed and a response provided to the site within an appropriate timeframe. If following this initial review eligibility is still unclear, the TrialNet Eligibility and Events Committee will review and adjudicate the situation.

3.2. Assignment of TrialNet Unique Identifier

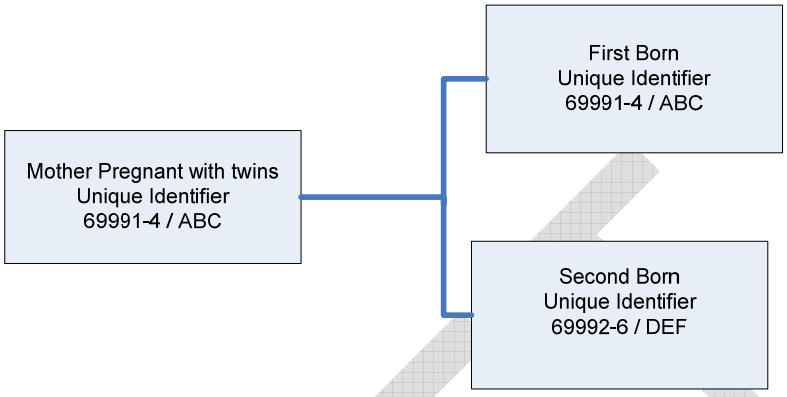
After informed consent is obtained, the subject will receive a Trial Net Unique Identifier, which consists ot a Screening Identification Number and 3 letters which will be used to identify the **child/ participant during the duration of the study**. The screening identification number contains 6 digits. The first 5 digits will be a sequential number, and the last number will be a check digit. The 3 letters are chosen randomly by the participant. This unique identifier per participant must remain the same thru out the duration of the study and all study forms.

The Coordinating Center will supply each participating clinical site with a screening number log containing a range of numbers to be used for participants at that clinical site (Appendix E). Each site will maintain a *Screening Identification Number Log* for tracking the screening numbers assigned to each participant (Appendix F). Once each month (at the end of the month), a copy of this log will be faxed to the Coordinating Center. **Only** the screening identification numbers portion of the log should be faxed to the Coordinating Center. **DO NOT FAX ANY INFORMATION THAT COULD POTENTIALLY BE LINKED TO THE PARTICIPANT HENCE, VIOLATING CONFIDENTIALTY**.

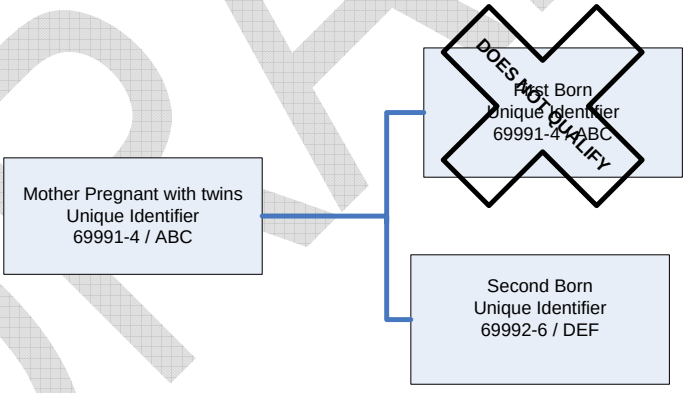
Entry A: Twin Delivery

If a mother in her 3rd trimester is pregnant with twins and plans to enroll both infants, she will receive a unique identifier (Screening number and 3 letters) at the Pregnant Woman Screening/Baseline visit. When the twins are born the mother will share her unique identifier with the first born and another unique identifier (screening number and 3 letters) will be

assigned to the second born child. These unique identifiers will remain the same for the duration of the study.



If the first born doesn't qualify for the study, the mother will remain with the same Unique Identifier assigned to her at the Pregnant Woman Screening/Baseline visit and the second born child will keep the Unique Identifier assigned to him/her when he/she was born.



In the case of twins, complete mother case report forms only once, but complete separate infant case report forms and blood draws for each child.

4. Entry A

Pregnant women in their third trimester will be enrolled through Entry A. Refer to the Schedule of Events for a complete list of and activities that are to be completed at this visit in the protocol and in Appendix G.

4.1. Eligibility Criteria

Inclusion Criteria:

Pregnant mothers in their third trimester are eligible if they:

- Have T1D or the child's father, or a full or half-sibling of the child has T1D. The mother may be eligible to screen through Entry A if she has T1D, has a spouse (biological father of the baby), or another child with diabetes (includes baby's half-sibling).
- Are 18 years of age or older
- Are in the third trimester of pregnancy (i.e. gestation is 24 weeks or longer). Only women on the last trimesters of pregnancy will be enrolled in the study.
- Have given informed consent and HIPAA Authorization
- Are willing to be assigned to either treatment group.

Exclusion Criteria:

Pregnant mothers are NOT eligible for enrollment into this study if they:

- have any condition the investigator believes will put the mother or her fetus at an unacceptable medical risk for participation in this study, such as Hypertension.
- have a known complication of pregnancy causing an increased risk for the mother or fetus prior to entry into the study, such as toxemia.
- have previously had multiple (2 or more) pre-term births (<36 weeks).
- will take omega-3 fatty acid supplementation or will provide omega-3 fatty acid supplementation to her infant independently during the study
- have diabetes and a known HbA1c greater than 9% **at anytime** during the pregnancy

4.2. Pregnant Woman Screening and Enrollment

Screening will consist of a clinic visit to be conducted after the 24th week of gestation for the pregnant woman. During the Pregnant Woman Screening and Enrollment Visit participants will:

- Be informed of the study requirements
- Complete the Volunteer Understanding Assessment
- Review and sign the Pregnancy and Newborn Child Enrolment Informed Consent
- Complete Medical History and Concomitant Medications
- Food Frequency Questionnaire
- Have a blood draw for HbA1c (if pregnant mother with diabetes - for eligibility criteria)
- Have blood drawn for Islets autoantibody, fatty acid analysis, inflammatory mediators, Vitamin D, CRP (if qualified)
- Randomization (If qualified)
- Drug Dispensation (after randomization)

For the informed Consent Process, refer to Chapter 3.

Refer to the Pregnant Women Screening/Enrollment Visit Checklist (NCL01) as guidance for activities and forms to be used during this visit

Pregnant women without diabetes can be enrolled after screening with no laboratory tests required if they meet eligibility criteria.

Pregnant women with diabetes will need an HbA1c test as part of eligibility screening prior to randomization. The HbA1c will be done locally. Results should be available the same day so the participant may be randomized at the same visit if she is eligible. If HbA1c results cannot be obtained the same day, HbA1c results obtained one month prior or less are acceptable. Record of the test and results should be kept in the site's research files for documentation. If the HbA1c is 9% or less, the participant is eligible to be in the study. If the HbA1c is above 9%, the participant is not eligible to participate at this time.

If the pregnant women is randomized, the mother will take the first dose of study capsules immediately after randomization at the visit and continue until the birth of the child. After the birth of the child, supplementation with the study capsules or formula will continue at least until the HLA of the infant is known. Specific guidelines for study substance dispensation and administration are provided in Chapter 11.

Infants of mothers who enrolled through entry A are required to meet eligibility criteria at the Infant Enrollment Visit before proceeding in the study.

Cord blood collection kits will be supplied to the parents at this visit. The site coordinator will add the TrialNet Parent Cord Blood Letter, the TrialNet Physician Cord Blood Letter, and a copy of the signed informed consent form to the kit. It is recommended that one kit be kept with the "*going to the hospital bag*" and one in another convenient location so that the parents remember to bring at least one kit with them to the delivery.

4.3. Infant Screening at Birth

At delivery, a sample of cord blood should be collected immediately after the birth of the child. Every attempt should be made to successfully collect and ship cord blood since this will be used to determine HLA Typing, Islet Auto antibodies, vitamin D, C-reactive protein and is also a valuable opportunity for analysis of fatty acids.

Refer to the Infant Delivery Checklist ENTRY A (NCL02) as guidance for activities and forms to be used during this visit

Specific cord blood collection procedures will vary by hospital, but there are a few main guidelines which may be taken into account.

The family's obstetrician should be educated and involved in the cord blood collection process in advance of the birth. TNCC has provided a sample Obstetrician Letter in the participant

materials which can facilitate this discussion. Communication should be maintained between the family and the delivery hospital so the logistics of collection and shipment will be well understood by all parties involved.

Use caution with the enclosed informed consent and applicable HIPAA laws. If there is no formal agreement with the delivery hospital's IRB, write "Do Not Add to Medical Record" clearly at the top of the consent. If you do have an agreement with the delivery hospital, abide by any guidelines that have been agreed upon.

When the family arrives at the hospital to deliver, they should give the cord blood kit to the obstetrician or other qualified staff member who plans to collect the blood. Qualified site coordinators may draw the blood if necessary, and if they are able to be present at the time of delivery. Cord blood may be collected before or after delivery of the placenta, depending on which method works best for the staff member. All specimens must be processed within 4 hours of the collection; therefore the site coordinator or other contact should be available at the time of delivery to process and ship the samples. Refer to the Specimen Collection and Shipping Instructions for details on processing, shipping, and information on drawing cord blood from twins.

If cord blood cannot be obtained at delivery, a heel stick needs be done at the Entry A Infant Screening Visit in order to determine the infants HLA.

4.4. Entry A Infant Screening (2 to 28 days old)

The Entry A Infant Screening Visit provides an opportunity to perform an infant medical history and limited physical exam to ensure that the participant is healthy enough to continue in the study. During this visit participants will:

Mother	Review and sign the Infant Enrollment Informed Consent
	Medical History, if nursing only
	Concomitant Medications
	Islet Auto antibodies (blood sample)
	Food Frequency Questionnaire
	Adverse Events
	Collect capsules
	If nursing, dispense capsules
	If not nursing, dispense formula

Infant	Medical History
	Limited Physical Examination
	Concomitant Medications
	If cord blood was not obtained, HLA typing and auto antibodies by heel stick for the baby
	Adverse Events

Refer to the Infant Screening Visit Checklist ENTRY A (NCL03) as guidance for activities and forms to be used during this visit.

If cord blood was not obtained during delivery, blood must be collected with a heel stick. This sample will be used to determine HLA typing and islet autoantibodies.

Mothers should bring all empty study substance bottles to this visit. They will be collected and documented and the appropriate study substance should be dispensed. Supplementation with the study capsules or formula will continue at least until the HLA of the infant is known. Specific guidelines for study substance dispensation and administration are provided in Chapter 11.

4.5. Entry A Infant Enrollment (approximately 4 weeks after birth)

The Entry A Infant Enrollment will take place approximately 4 weeks after the HLA blood collection (cord blood or heel stick). During this visit the Infant ‘s eligibility will be evaluated. Activities to be performed

Infant	Review Eligibility Criteria (Eligibility report and protocol)
	Medical History
	Concomitant Medications
	Immunization Record
	Adverse Events

Mother	Medical History – all mothers
	Concomitant Medications – all mothers
	Food Frequency Questionnaire – all mothers
	Islet Auto antibodies (blood sample)
	Adverse Events
	Blood work - all mothers
	Collect capsules/formula
	If nursing, dispense capsules
	If not nursing, dispense formula

Refer to the Infant Enrollment Visit Checklist ENTRY A (NCL05) as guidance for activities and forms to be used during this visit.

The Eligibility Report will be available on the TrialNet website approximately 3-4 weeks after blood collection (cord blood or heel stick). The eligibility report **only takes into account T1D family history and HLA results**, therefore the “yes” or “no” indicated on the report should be

integrated with other criteria to determine if the infant may continue in the study (Appendix H). Infants are required to meet all the eligibility criteria to be included in the study.

If the infant is eligible to continue, the Entry A Infant Enrollment will take place, and in the event the infant is not eligible, a Non-Qualified Debriefing Visit should be scheduled.

For eligibility take into account:

- If the infant has two 1st or 2nd degree relatives with T1D, and no protective allele, he or she is eligible to continue in the pilot.
- If the infant has one 1st or 2nd degree relative with T1D, and high risk HLA type, he or she is eligible to continue in the pilot.
- If the infant has one 1st or 2nd degree relative with T1D, and low risk HLA type, he or she is not eligible to continue in the pilot.
- An infant with a protective allele, regardless of multiplex family T1D status is not eligible to continue in the pilot.

If the participant meets all the eligibility criteria, he/she will be assigned the same color study substance as the mother. This also applies for twins.

4.6. Entry A Screening Combined with Infant Enrollment

If cord blood was collected at delivery time and HLA results are available before the 28 days after delivery visit window, some sites may prefer to combine the Entry A 2 to 28 Day Screening Visit with the Entry A Infant Enrollment Visit.

TNCC will send this eligibility report via email, which will be generated using NPP01 and CHORI HLA lab results. It is recommended that the visit be scheduled as early as possible, though at least by 25 days of age to allow some room for error. Screening assessments and draws should be done before any Enrollment assessments. The participant will not be

randomized at the end of this visit, but instead will be assigned the same color study substance as the mother.

Refer to NCL10 for assessments and blood draws to be completed.

5. Entry B

Infants 2 days to 5 months of age will be enrolled through Entry B.

5.1. Eligibility Criteria

Inclusion Criteria:

Infants are eligible for enrollment if they:

- Are less than six months of age at the time of enrollment. When screening infants take into account that the HLA results will take approximately 4 weeks to be available. The infant needs to be less than six months when they are randomized. Screen infants between 2 days and 5 months old.
- Have a mother, father or a full or half-sibling with T1D
- Have a HLA DR3 or DR4 allele OR have another 1st or 2nd degree relative with T1D AND they do not have a protective HLA allele (DQB1*0602 or DRB1*0403

Exclusion Criteria:

Infants are NOT eligible for enrollment into this study if they:

- Have any condition the investigator believes will put the infant at an unacceptable medical risk for participation in this study
- Have a mother with a condition the investigator believes will put her or the infant at an unacceptable medical risk for participation in this study
- Have a nursing mother who will take omega-3 fatty acid supplementation or a parent or legal guardian who will provide supplementation to his/her infant independently during the study (if infant entered prenatally, this exclusion criteria is assessed only once when the pregnant mother entered the study)

- Have a protective HLA allele (DQB1*0602 or DRB1*0403)
- Were born prior to 36 weeks gestation or require a pre-term infant formula

First degree relatives of the infant include the infant's mother, father, full siblings, and half siblings. Second degree relatives of the infant include maternal aunts and uncles, paternal aunts and uncles, maternal grandparents, and paternal grandparents. All first and second degree relatives must be relatives by blood (not by marriage).

5.2. Entry B Infant Screening (2 days to 5 months of age)

Screening will consist of a clinic visit to be conducted when the infant is two days to five months of age. During the Infant Screening Visit participants will:

Mother, Father or legal guardian	Be informed of the study requirements
	Complete the Volunteer Understanding Assessment
	Review and sign the Infant enrollment Informed Consent and HIPAA
	Medical History, only if Nursing
	Concomitant Medications, only if nursing
	Food Frequency Questionnaire, only if nursing
	Islet Auto antibodies (blood sample) – all mothers

Infant	Review Eligibility Criteria (Eligibility report and protocol)
	Medical History and limited Physical Examination
	Concomitant Medications
	Heel stick (HLA and Biochemical autoantibodies)
	Assigned Unique Identifier (Screening number and 3-letter)

Refer to the Infant Screening Visit Checklist ENTRY B (NCL04) as guidance for activities and forms to be used during this visit. For Consent Process information refer to Chapter 3.

Fathers, guardians, or other family members may enroll their infant through Entry B if the mother is deceased or unable to be contacted. They will follow the Entry B non-nursing path and omit any mother blood draws that are otherwise required.

Infants should meet all of the inclusion criteria and none of the exclusion criteria **except** for HLA determinants at the infant screening visit. A heel stick will be done at the Infant Screening Visit to determine full eligibility. Results will be available in approximately 4 weeks. The site coordinator should check the website in approximately 3 to 4 weeks to establish whether or not the participant is eligible.

Infants will be assigned a Unique Identifier with a Screening ID from the site's Screening Log and 3 letters chosen by the mother, father or legal guardian. .

5.3. Entry B Infant Enrollment (4 weeks after HLA blood collection)

The Eligibility Report will be available on the TrialNet website approximately 3-4 weeks after blood collection (cord blood or heel stick). The eligibility report **only takes into account T1D family history and HLA results**, therefore the "yes" or "no" indicated on the report should be integrated with other criteria to determine if the infant may continue in the study. Infants are required to meet all the eligibility criteria to be included in the study.

Take into account the following information regarding HLA to determine participants eligibility:

- If the infant has two 1st or 2nd degree relatives with T1D, and no protective allele, he or she is eligible to continue in the pilot.

- If the infant has one 1st or 2nd degree relative with T1D, and high risk HLA type, he or she is eligible to continue in the pilot.
- If the infant has one 1st or 2nd degree relative with T1D, and low risk HLA type, he or she is not eligible to continue in the pilot.
- An infant with a protective allele, regardless of multiplex family T1D status is not eligible to continue in the pilot.

The site coordinator should check the eligibility report before bringing the participants to the visit.

- If the infant is eligible to continue in the study, an Infant Enrollment Visit will be scheduled. Nursing mothers should be reminded to bring a breast milk sample to this visit.
- In the event the infant is not eligible, a Non-Qualified Debriefing Visit should be scheduled or participants may choose to complete the Non-Qualified Debriefing Visit by phone since there is no study substance to return or other assessments to complete.

Summary of activities for this visit:

Infant	Review Eligibility Criteria (Eligibility report and protocol)
	Medical History
	Concomitant Medications
	Food Introduction History
	Immunization Record
	Randomization to study
	Adverse Events

Mother	Medical History – all mothers
	Concomitant Medications – if nursing
	Food Frequency Questionnaire – if nursing
	Blood work – only if nursing (fatty acids, inflammatory mediators, Vitamin D and C-Reactive Protein)
	Breast Milk Collection
	If nursing, dispense capsules
	If not nursing, dispense formula

Refer to the Infant Enrollment Visit Checklist ENTRY B (NCL06) as guidance for activities and forms to be used during this visit.

Eligible infants will be randomized at the end of the visit. If the mother is nursing, study capsules will be dispensed. The mother will take the first dose of study capsules immediately after randomization at the visit. If the mother is NOT nursing, study formula will be dispensed and the participant will be asked to start the formula as soon as possible. Specific guidelines for study substance dispensation and administration are provided in Chapter 11.

All Screening and Enrollment Visits must be conducted within the timeframe specified in the NIP Diabetes Protocol. Follow up visits may be scheduled two weeks before or after the indicated age of the child.

The mother may choose to combine the Entry A Infant Screening and Enrollment visits if cord blood was successfully collected and shipped at the time of delivery, and also successfully processed by the lab

5.4. Entry B Infant Enrollment Visit combined with 3 or 6 Month Old Follow-up visits

The Entry B Infant Enrollment Visit may fall within the visit window of the 3 or 6 month Follow-up Visit. For example, if an infant enters through Entry B and is enrolled at 6 months of age, he or she will also be within the visit window for the 6 Months of Age Follow-up Visit. Entry B Infant Enrollment Visit Checklist (NCL06) details the forms, assessments and

activities that need to be completed for this combined visit. The 3 month follow-up visit would not be conducted for this participant because that time point had already passed. The participant would next return for the 9 Months of Age Follow-up Visit.

In the case of another younger participant, it is possible that the 3 Month Follow-up Visit would be combined with Entry B Infant Enrollment and their next schedule visit would be the 6 Months of Age Follow-up Visit.

5.5. Non -Qualified Debriefing Visit (Entry A or Entry B)

If the participant is ineligible, he or she should bring the remaining supply of study substance to the Non-Qualified Debriefing Visit. The site coordinator should also inform the participant of their HLA risk status and ensure that they understand the relative meaning of a lower risk HLA. A low risk HLA means that the participant has a lower risk of developing type 1 diabetes compared to other participants who screen for this study. It does not mean that they have no risk of developing T1D in the future. The child should continue to attend regular doctor and screening visits as they would irrespective of the screening results.

If the participant prefers to conduct the Non-Qualified Debriefing Visit over the phone, they may arrange for a pre-paid Fed-Ex label to return study substance to the site. A discussion will take place regarding the infant's HLA status and the appropriate forms will be completed by the site coordinator.

Refer to the Non-Qualified Debriefing Visit Checklist (NCL07) as guidance for activities and forms to be used during this visit.

CHAPTER 7 FOLLOW-UP

1. Follow-Up Visits

Follow up visits take place based on infants age. The first follow-up visits will take place after infant enrollment when the infant is 3 months or 6 months of age. The age of the infant at the first follow-up visit will vary according to the age of the infant when he or she entered the study. Visits will take place at 3 month intervals until 24 months of age. After 24 months of age, visits will take place every 6 months until 36 months of age. Visits may be conducted within the two weeks window. Details regarding visits that take place after 36 months of age will be provided closer to the transition time to the full study.

Mothers will attend all visits; however infants are only required to attend the 6, 12, 18, 24, 30, and 36 month visits. In the event of an emergency, non-nursing mothers may opt to conduct visits 3, 9, 15, or 21 months visits by phone, though this option should only be used in extenuating circumstances.

2. 3 Months Old Visit (Mother only)

Summary of activities for this visit

Mother, only if nursing	Medical History
	Concomitant Medications
	Food Frequency Questionnaire
	Breast Milk Collection
	Collect empty study capsules
	If nursing, dispense capsules
	If not nursing, dispense formula

This information will be gathered about the infant:

Infant	Concomitant Medications
	Food Introduction History
	Immunization Record
	Adverse Events

Refer to the 3, 9, 15 and 21 Month Old Visit Checklist (NCL08) as guidance for activities and forms to be used during this visit.

3. 6 Months Old Visit (Mother and Infant visit)

Summary of activities for this visit

Mother, only if nursing	Medical History
	Concomitant Medications
	Food Frequency Questionnaire
	Breast Milk Collection – fatty acid analysis
	Adverse Events
	Collect empty study capsules
	If nursing, dispense capsules
	If not nursing, dispense formula

This information will be gathered about the infant:

Infant	Medical History
	Limited Physical Examination
	Local Blood Glucose Testing
	Blood draw – Islet atutoantibodies, fatty acid analysis, inflammatory mediators, vitamin D, CRP
	Concomitant Medications
	Food Introduction History
	Immunization Record
	Adverse Events

Refer to the 6, 12, 18 and 24 Month Old Visit Checklist (NCL09) as guidance for activities and forms to be used during this visit.

At the 6 month visit, nursing mothers will bring a breast milk sample for analysis.

4. 9 Months Old Visit (Mother only)

Summary of activities for this visit

Mother, only if nursing	Medical History
	Concomitant Medications
	Food Frequency Questionnaire
	Breast Milk Collection
	Collect empty study capsules
	If nursing, dispense capsules
	If not nursing, dispense formula

This information will be gathered about the infant:

Infant	Concomitant Medications
	Food Introduction History
	Immunization Record
	Adverse Events

Refer to the 3, 9, 15 and 21 Month Old Visit Checklist (NCL08) as guidance for activities and forms to be used during this visit.

5. 12 Months Old Visit (Mother and Infant visit)

Summary of activities for this visit

Mother, only if nursing	Medical History
	Concomitant Medications
	Food Frequency Questionnaire
	Breast Milk Collection – fatty acid analysis
	Adverse Events
	Collect empty study capsules
	If nursing, dispense capsules
	If not nursing, dispense formula

This information will be gathered about the infant:

Infant	Medical History
	Limited Physical Examination
	Local Blood Glocuse Testing
	Blood draw – Islet atutoantibodies, fatty acid analysis, inflammatory mediators, vitamin D, CRP, tetanus antibody and cellular response
	Concomitant Medications
	Food Introduction History
	Immunization Record
	Adverse Events

Refer to the 6, 12, 18 and 24 Month Old Visit Checklist (NCL09) as guidance for activities and forms to be used during this visit.

At the 12 month visit, nursing mothers will bring a breast milk sample for analysis If 2 or more autoantibodies are present on or after the 12 month visit, 1 or 2 months later a confirmation blood drawn will be done. If the same 2 autoantibodies are present at both visits, the child will discontinue the study substance and withdraw from the study.

6. 15 Months Old Visit (Mother visit only)

This information will be gathered about the infant:

Infant	Concomitant Medications
	Food Introduction History
	Adverse Events
	Collect empty study capsule bottles
	New study substance will be supplied

Refer to the 3, 9, 15 and 21 Month Old Visit Checklist (NCL08) as guidance for activities and forms to be used during this visit.

7. 18 Months Old visit (Mother and Infant visit)

This information will be gathered about the infant:

Infant	Medical History
	Limited Physical Examination
	Local Blood Glucose Testing
	Blood draw – Islet atutoantibodies, fatty acid analysis, inflammatory mediators, vitamin D, CRP, tetanus antibody and cellular response
	Concomitant Medications
	Food Introduction History
	Immunization Record
	Collect empty study capsule bottles
	New study substance will be supplied
	Adverse Events

Refer to the 6, 12, 18 and 24 Month Old Visit Checklist (NCL09) as guidance for activities and forms to be used during this visit.

If 2 or more autoantibodies are present on or after the 12 month visit, 1 or 2 months later a confirmation blood drawn will be done. If the same 2 autoantibodies are present at both visits, the child will discontinue the study substance and withdraw from the study.

8. 21 Months Old visit (Mother visit only)

This information will be gathered about the infant:

Infant	Concomitant Medications
	Food Introduction History
	Adverse Events
	Collect empty study capsule bottles
	New study substance will be supplied

Refer to the 3, 9, 15 and 21 Month Old Visit Checklist (NCL08) as guidance for activities and forms to be used during this visit.

9. 24 Months Old visit (Mother and Infant visit)

This information will be gathered about the infant:

Infant	Medical History
	Limited Physical Examination
	Local Blood Glucose Testing
	Blood draw – Islet atutoantibodies, fatty acid analysis, inflammatory mediators, vitamin D, CRP, tetanus antibody and cellular response
	Concomitant Medications
	Food Introduction History
	Immunization Record
	Collect empty study capsule bottles
	New study substance will be supplied
	Adverse Events

Refer to the 6, 12, 18 and 24 Month Old Visit Checklist (NCL09) as guidance for activities and forms to be used during this visit.

If 2 or more autoantibodies are present on or after the 12 month visit, 1 or 2 months later a confirmation blood drawn will be done. If the same 2 autoantibodies are present at both visits, the child will discontinue the study substance and withdraw from the study.

10. 30 Months Old visit (Mother and Infant visit)

This information will be gathered about the infant:

Infant	Medical History
	Limited Physical Examination
	Local Blood Glucose Testing
	Blood draw – Islet atutoantibodies, fatty acid analysis, inflammatory mediators, vitamin D, CRP, tetanus antibody and cellular response
	Concomitant Medications
	Food Introduction History
	Immunization Record
	Collect empty study capsule bottles
	New study substance will be supplied
	Adverse Events

Refer to the 6, 12, 18 and 24 Month Old Visit Checklist (NCL09) as guidance for activities and forms to be used during this visit.

If 2 or more autoantibodies are present on or after the 12 month visit, 1 or 2 months later a confirmation blood drawn will be done. If the same 2 autoantibodies are present at both visits, the child will discontinue the study substance and withdraw from the study.

11. 36 Months Old visit (Mother and Infant visit)

This information will be gathered about the infant:

Infant	Medical History
	Limited Physical Examination
	Local Blood Glucose Testing
	Blood draw – Islet atutoantibodies, fatty acid analysis, inflammatory mediators, vitamin D, CRP, tetanus antibody and cellular response
	Concomitant Medications
	Food Introduction History
	Immunization Record
	Collect empty study capsule bottles
	New study substance will be supplied
	Adverse Events

Refer to the 6, 12, 18 and 24 Month Old Visit Checklist (NCL09) as guidance for activities and forms to be used during this visit.

If 2 or more autoantibodies are present on or after the 12 month visit, 1 or 2 months later a confirmation blood drawn will be done. If the same 2 autoantibodies are present at both visits, the child will discontinue the study substance and withdraw from the study.

12. Missed Visits

If a participant misses a scheduled visit, every effort should be made to reschedule the visit within the permissible window period surrounding the original visit date. If the visit is rescheduled within this timeframe, no further actions need to be taken, and the visit should go on as planned. If the visit is not rescheduled within this window, every effort should be made to bring the participant into the clinic as soon as possible. If the participant comes into the clinic beyond the allowable visit window, the Missed Visit Form (NPP17) should be completed.

Example 1: A participant is scheduled to have his Month 9 visit on January 1. The participant is supposed to then have his Month 12 visit on April 1. The participant misses the visit on January 1 and is unable to come into the clinic at any time before April 1. In this situation the Month 9 visit is considered missed, and the Missed Visit Form (NPP17) needs to be completed to document this information. The participant then continues with the Month 12 visit on April 1 as scheduled.

The visit schedule is determined based on the **age of the infant**. Therefore, it is possible to establish the exact date and corresponding window period for every visit the participant will make from randomization until the end of the study.

Every effort should be made to contact participants who fail to attend their follow-up visits in order to ensure that they are in satisfactory health and to encourage them to continue with future study follow-up visits. This will entail, at a minimum, three telephone contact attempts and two written attempts with return receipt requests. Research staff at each of the sites is responsible for keeping participant contact information up to date at every study visit.

CHAPTER 8 RANDOMIZATION

1. Overview

Only participants complying with all the inclusion/exclusion criteria will be randomized to the NIP Pilot trial. The information from the screening and enrollment data collection forms will be reviewed to assess whether a participant is eligible to be randomized and enrolled in the study. Participants who do not meet all of the inclusion criteria or have one of the exclusion criteria will be referred back to their physician for standard education, treatment, and care. Participants not eligible may be offered the opportunity to participate in another TrialNet study, if one is available.

2. Randomization

After the participant have signed the Informed Consent Form completed the screening visits and enrollment procedures, have met all of the inclusion criteria and none of the exclusion criteria, they will be randomized to one of the two study groups: DHA study substance or control. Neither the coordinating center nor the participating sites will know the treatment group assignment. The Coordinating Center will maintain the list of participant randomization assignments.

2.1. Randomization Method

The Coordinating Center will specify the randomization schedule for the study sites. Participants will be randomized, in approximately equal numbers, to the two arms of the study. The randomization method will be stratified by TrialNet study site. This approach ensures that the number of treatment group assignment will be approximately balanced within each site. Manufacturers devised 4 color codes for the two treatment groups. The Randomization color code will in no way reflect the treatment group to which the participant has been assigned. After a participant is randomized, the study coordinator will contact the site pharmacist to obtain the study medication (if applicable).

In the event that **multiple siblings** are entered from a single family, only the first family member will count towards the recruitment goal of 90 participants. The treatment randomly

assigned to the first family member will also be assigned to all other family members who enter. This is due to statistical considerations since family members do not represent independent observations.

2.2. Randomization Procedure

There are two different randomization systems, Mother (Entry A) or Infant (Entry B). This is different than other studies which only have one randomization system.

Mother (Entry A): Pregnant women on Entry A will be randomized at the Pregnant Woman Screening/Eligibility visit if they comply with all the Inclusion/Exclusion Criteria. Once the baby is born, the infant **must** qualify to the study in order to be given study substance. The infant must comply with all the Inclusion/Exclusion criteria. The infant doesn't need to be randomized again; the study substance given to the infant will be the same as the mother (same color).

Infant (Entry B): infants will be randomized at the Entry B Enrollment visit.

If a pregnant woman is not randomized in Entry A, the infant can be tested for eligibility in for Entry B.

2.3. Assigned Schedule of Assessments

A schedule of assessments is provided in Appendix G of this manual and Appendix A of the protocol. There will be slight variations between pregnant women who enroll via entry A and infants who enroll via entry B.

2.4. Web Randomization System

Before logging into the TrialNet Web Randomization System, ensure the following:

- Participant meets **all** of the inclusion and **none** of the exclusion criteria for the study
- Participant has reviewed and signed the applicable informed consent
- Participant has completed all screening and enrollment procedures.

- You have completed all the applicable Data Forms.

If all of these criteria have been met, the participant is eligible for randomization and the TrialNet Web Randomization System should be accessed. The system is operable 24-hours per day, 7 days a week. Refer to Chapter 9 for instructions on using the Web Randomization System.

CHAPTER 9 TRIALNET WEB RANDOMIZATION SYSTEM

This chapter contains instructions on performing a mock randomization for certification and randomizing a participant into the NIP Pilot Trial.

1. **System requirements**

   You will require:

   1. Computer with an internet browser and internet access.
   2. Access to the TrialNet secure website.
   3. NIP Diabetes Pilot Web Randomization System pass-phrase (8 characters minimum).
   4. Site-specific NIP Diabetes Pilot screening log to choose an unused Screening ID.
   5. Printer with paper.

2. **Performing a MOCK Randomization for Certification**

   Log In

   Enter Screening ID

   Confirm Eligibility and Randomize

   View Schedule of Assessments

   Log Out

2.1. Log In

- Provide the TNCC with your pass-phrase to access the system. The TNCC will notify you when your pass-phrase has been activated. Web randomization pass-phrases cannot be shared among site staff. *Note: the pass-phrase may be any length and consist of letters and/or numbers, include spaces, and are case sensitive.*
- Once your pass-phrase has been activated, log into the TrialNet Website under your username at: www.diabetestrialnet.org
- Click on Studies/Active Studies/NIP Diabetes Pilot
- Under the header "Resources", look for Randomization and choose Mother Entry A or Infant Entry B

- Enter your pass-phrase and hit enter.
- Note that throughout the mock randomization, the banner at the top of the page should say **"Mock Randomization**". If not, contact the TNCC.

2.2. Enter Screening ID

- Note that the mock randomization web pages are identical to the live randomization system, with the exception that you are assigned to the fictitious site number 9999 with corresponding fictitious screening IDs and lab results.

- The "Overview" page contains 5 columns of screening IDs for site number 9999.
    - The first column (Eligibility in progress) contains participants whose eligibility criteria are still being evaluated (i.e. required lab results have been received but the eligibility questions have not been answered).
    - The second column (Not eligible) contains all participants who have been screened at the site but are not eligible.
    - The third column (Sibling/Family) contains information about other family members already participating in the study
    - The fourth column (Eligible, not randomized) contains participants who have met all of the eligibility requirements but have not been randomized.
    - The fifth column (Randomized) contains all randomized participants.

- For the purposes of the mock randomization, either click on one of the screening IDs listed in column one (Eligibility in progress) or enter one of these IDs into the space provided. *Note: if you choose to enter the screening ID, you must include the "-" (i.e. 9901-5).*

2.3. Confirm Eligibility and Randomize

- The "Subject Information" page contains a list of eligibility criteria for this study.

- Once you have answered all of the eligibility questions, click on "Save my changes".

- The system will identify at the top of the page whether or not the participant is eligible. If the participant is ineligible, a red asterisk (*) will appear on the left hand side of the page next to the violated eligibility criterion.

- If the participant is eligible and the "Save my changes" button is clicked, the participant will NOT be randomized and their screening ID will be moved to the fourth column (Eligible, not randomized) of the "Overview" page. For the purposes of the mock randomization, click on "Randomize now".

- The eligibility criteria will be saved and the participant will be assigned a randomization color, which will appear at the top of the page. Once the participant is randomized, their screening ID will be moved to the fifth column (Randomized) of the "Overview" page.

- Note that once you have successfully completed the mock randomization, the word "certified" will appear in the upper right hand corner of the page under your name.

2.4. Log Out

- In order to access the live randomization system, log out of the system by clicking on "Log out" at the top of the page, and log back into the system. Note that when you are in the live randomization system, the banner at the top of the page will NOT say "Mock Randomization". *Note: if the system automatically prompts you for a password during the mock randomization, you have been logged out of the system. If you log back in, you will be in the live randomization system if you successfully completed the certification process. If you would like to repeat the mock randomization, please contact the TNCC.*

- Note that any page may be printed by clicking on "Print this page" at the top of the page.

In order to move from the Mock Randomization to the real system, you will need to successfully complete one randomization in either the Entry A or Entry B system, click on "Log out," (located in the green toolbar as part of "Your Options") and then log back in.

3. Randomizing a Participant into the NIP Pilot Trial

Log In

Enter Screening ID

Confirm Eligibility and Randomize

View Schedule of Assessments

Log Out

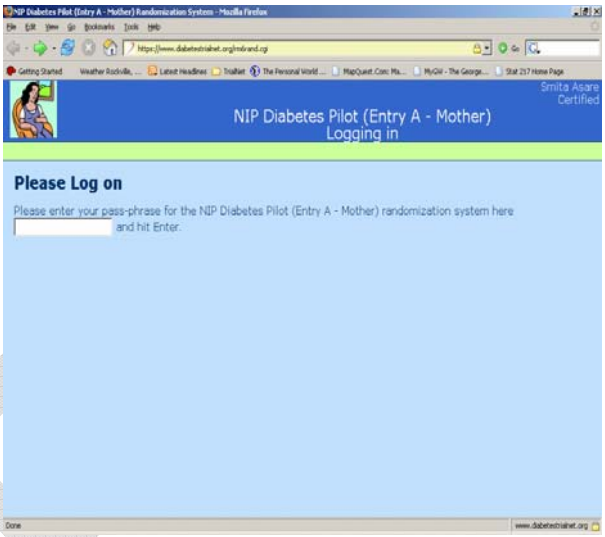
3.1. Log In

- Log into the secure TrialNet Website under your username at: www.diabetestrialnet.org

- Click on Studies/Active Studies/NIP Diabetes Pilot. Under the header section Resources click on one of the links next to Randomization: Mother entry A or Infant (entry B).

- There are two Web Randomization system interfaces:
    1. 3er trimester pregnant mother (Entry A)
    2. Infant (Entry B)

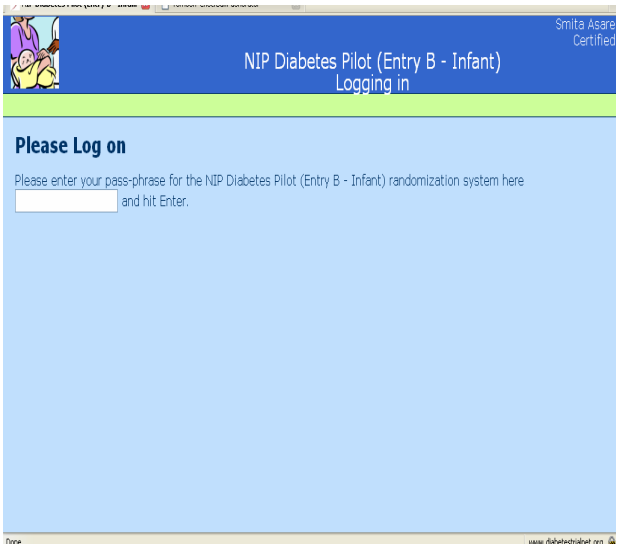
For the Entry A log in page:



Always check for the following:

- ✓ Your name appears in the upper right-hand corner
- ✓ Under your name it will indicate your certification status as either "Not certified" or "Certified"
- ✓ The web header in the center states "NIP Diabetes Pilot (Entry A – Mother)"
- ✓ A pregnant mother graphic is in the left-hand corner
- ✓ Type your pass phrase and hit <Enter>.

For the Entry B log in page



Always check for the following:

- ✓ Your name appears in the upper right-hand corner
- ✓ Under your name it will indicate your certification status as either "Not certified" or "Certified"
- ✓ The web header in the center states "NIP Diabetes Pilot (Entry B – Infant)"
- ✓ An infant graphic is in the left-hand corner
- ✓ Type your pass phrase and hit <Enter>.

3.2. Enter Screening ID

The "Overview" page contains 5 columns of screening IDs for your site. *Note: the valid screening IDs for your site are located on the Screening Number Log provided by the TNCC.*

Eligibility in progress	Contains a list of Screening IDs of participants whose eligibility is still being evaluated.
Not eligible	Contains a list of Screening IDs of participants who were found to be NOT eligible. If eligibility changes, you may still modify their eligibility criteria. (This list may include siblings who were found to be *not* eligible).
Sibling/family	A list of Screening IDs of ***eligible*** participants who have an existing sibling already randomized to a treatment group and color. If placed in this column, the participant may enroll in the study. They must be assigned the same treatment color as their first eligible sibling (who may have entered through pathway A or B). The system recognizes these individuals as siblings because you would have entered this information with the correct Screening ID in question Entry A: B6a or Entry B: B8a. Double check this information on your end since we don't have a double check built into the system. Click "Overview" to go back to main page
Eligible, not randomized	A list of Screening IDs of eligible participants. These participants have not been randomized for various reasons (e.g. not agreed to participate, still reviewing the consent or other information or have not completed all baseline enrollment activities). Many times these will be screened participants who are waiting on the Infant Eligibility Report to possibly be enrolled. When a participant is randomized, be sure to do the randomization at the end of the enrollment visit. It should be done after doing all the baseline tests and after completing all the forms. You should have a clear mindset instead of knowing which randomization color is assigned when doing baseline activities. Click "Overview" to go back to main page
Randomized	Once a participant is randomized, their information is set and cannot be altered. The Screening IDs under this column cannot be altered Entry A and Entry B participants are both listed here and are shared between the two randomization systems. Click "Overview" to go back to main page

- To randomize a new participant, either click on the screening ID of that participant listed in column one (Eligibility in progress) or enter the ID into the space provided. *Note: if you choose to enter the screening ID, you must include the "-" (i.e. 69901-5).* Note that if the screening ID of the participant you wish to randomize is not displayed in column one, the required lab results have not been received and you will not be allowed to randomize the participant. If this is incorrect, please contact the TNCC immediately.

- To randomize a participant who's eligibility criteria you have previously entered and saved, either click on the screening ID of that participant listed in column four (Eligible, not randomized) or enter the ID into the space provided.

- To view a previously randomized participant's eligibility criteria, randomization color, and/or schedule of assessments, either click on the screening ID of that participant listed in column five (Randomized) or enter the ID into the space provided.

3.3. Confirm Eligibility and Randomize

- The "Subject Information" page contains a list of eligibility criteria for this study.

- Identify:
  - All the inclusion/exclusion criteria are correctly answered and complying with the protocol.
  - *Note: all questions must be answered correctly and all required lab results must be received in order to successfully randomize a participant. If any information is missing or violates an eligibility criterion you will NOT be allowed to proceed with randomization.*

- Once you have answered all of the eligibility questions, click on "Save my changes".

- The system will identify at the top of the page whether or not the participant is eligible. If the participant is ineligible, a red asterisk (*) will appear on the left hand side of the page next to the violated eligibility criterion.

- If the participant is eligible and the "Save my changes" button is clicked, the participant will NOT be randomized and their screening ID will be moved to the four column (Eligible, not randomized) of the "Overview" page. Click on "Randomize now" to randomize the participant.

- The eligibility criteria will be saved and the participant will be assigned a randomization color, which will appear at the top of the page. This number must be recorded on the appropriate Form. Once the participant is randomized, their screening ID will be moved to the fifth column (Randomized) of the "Overview" page.
-

3.4. Log Out

- Log out of the system by clicking on "Log out" at the top of the page when finished.

CHAPTER 10 STUDY SUBSTANCE

This chapter provides descriptions of the study substance being used in the NIP Pilot Trial as well as shipping, ordering, returning, and accountability information for these products. The study substance will be provided by EMINENT Services Corporation. See Appendix I for some examples of Eminent and local Pharmacy Forms to be used during the study.

1. EMINENT Services Corporation

EMINENT Services Corporation is Good Manufacturing Practice certified and serves as the central distributor for TrialNet studies. EMINENT receives, stores, packages, labels, and ships substances and nutritional products as necessary, for studies and processes and destroys returned drug and nutritional products. Accurate records are maintained of all product labeling, packaging and shipment tracking. Products are tracked by EMINENT to their final destination, whether it is the participant, back to the warehouse, or product destruction.

EMINENT hours are Monday through Friday, 8:00 AM to 5:00 PM Eastern Time (North America). A pharmacist can be reached during these normal business hours at phone number: (240) 629-1972. For all other emergencies during the non-business hours, weekends, and holidays, sites may contact EMINENT using the clinical emergency hot-line **(888) 321-4364 or (240) 629-1972 (Option 8)**.

Contact Information:

Type 1 Diabetes TrialNet – NIP Diabetes Pilot (TN-06)
c/o EMINENT Services Corporation
7495 New Technology Way
Frederick, MD 21703-9401
Tel: (240) 629-1972
Fax: (240) 629-3298
E-mail: service@emiserv.com

2. Study Substance

2.1. Description of Study Substance

FORMULA: The *control* formula used in this study is a commercially available formula marketed under the name Enfamil Lipil®. This formula delivers 3.4 mg DHA per ounce. The *intervention* formula used in this study is not yet commercially available. It delivers 10.0 mg DHA per ounce. Both are manufactured by Mead Johnson Nutritionals, Inc.

CAPSULES: The *control* study substance is a gelatin capsule containing a neutral vegetable oil. The *intervention* study substance is a gelatin capsule containing DHASCO®-S oil (which is commercially available). The DHASCO®-S oil is derived from microalgae in vats (no mercury or pesticide contaminants). The expectation is that there will be similar absorption of DHA contained in the capsules versus DHA oil derived from fish. The FDA has granted GRAS (*Generally Recognized as Safe*) status to DHASCO®-S and it has been approved for addition to infant formulas. Several infant formulas containing DHASCO®-S are now commercially available in the U.S. Both are manufactured by Martek Biosciences Corp.

2.2. Packaging and Shipment Information

FORMULA: The study formula is supplied in 32 ounce ready-to-use cans. There are six cans to a case To maintain the blind, they will be dispensed to the participant by lot number and label color according to the randomization number assigned.

Product Code/ Color Code/ Production Run	**Label Color**
3370-174-XX	Gray
3370-199-XX	Yellow
3370-673-XX	Red
3370-794-XX	Orange

CAPSULES: The study substance / capsules is supplied in bottles of 100 capsules. To maintain the blind, they will be dispensed to the participant according to randomization color assigned.

Label Color
Gray
Yellow
Red
Orange

2.3. Initial Shipment of Study Substance

The Coordinating Center will arrange for all sites to receive an initial shipment of study capsules and formula once the site has been certified by TrialNet Coordinating Center. The initial shipment will contain

- 40 cases of formula (10 cases of each color) and
- 140 bottles (35 bottles of each color).

2.4. Ordering Study Drug

Study substance inventory must be monitored closely to ensure that an adequate supply is on site well in advance of the participant's visit. Each site will be responsible for ordering directly from EMINENT. Take into account when reordering study substance that t**here is a 2 week turn around from order to delivery.**

To order study formula and/ or capsules, please complete an *Agent Request Form* and FAX to (240) 629-3298.

The **STUDY PRODUCT REQUEST FORM** can be found on the TrialNet website under NIP/Resources/View all study documents/Essential Documents Binder/TN06 Study Product Request Form. The following is an example on how to fill out the Study Product Request Form for study formula:

Instructions for Completing an *Agent Request Form – Formula*

1. When completing an *Agent Request Form – Formula,* please clearly print all requested information, except for the box labeled For Eminent Use only.

2. Enter the site number, clinical investigator's name, and other required information in the top, middle section of the form.

3. Each line of the order should contain only one item. Complete each line as follows:

a. Protocol number (pre-printed Protocol TN06)

b. Current inventory (at the site)

c. Quantity required

4. . ONLY the designated clinical site contact may sign and date the order form.

5. The shipping address must be printed clearly. Do not use a rubber stamp, since this usually does not yield a sharp image and does not photocopy or transmit well by FAX.

6. The completed form may be FAXED to (240) 629-3298 or sent via express courier to the EMINENT Services Corporation.

7. Retain a copy of the order so that verification of the order can be confirmed upon arrival of the shipment. Retain a copy of the shipping receipt upon delivery. There will be instruction on the shipping receipt for confirmation of delivery (fax to Eminent to confirm that shipment was received and condition of shipment noted).

2.5. Receipt and Storage

When study substances are received at the clinical site from EMINENT, IT IS IMPORTANT THAT IT BE INSPECTED AS SOON AS POSSIBLE. Carefully check items received

against the packing slip, noting container sizes, quantities, and lot numbers. EMINENT should be notified IMMEDIATELY if there are any discrepancies.

Place study substances in an appropriate, limited access storage area. This area must be kept separate from routine stock. Room temperatures are to be measured daily except weekends and holidays at a minimum and recorded in the temperature log provided or a site specific log. Note that study formula and study capsules should be stored out of direct sunlight and at the following temperatures:

FORMULA:

- Long term storage: 68-80° F
- As long as there is no damage to the seal or container, the product should remain commercially sterile.

CAPSULES

- Long term storage: dry locked compartment at 60-75° F.

2.6. Study Substance Delivery and Storage at Clinical Site

Each formula case is 8" high x 7 " wide x 10 5/8" deep. The cases will be delivered on a pallet and shrink-wrapped. They will be delivered to the shipping and receiving or loading dock at your hospital/clinical site. So, it's very important for the Site Coordinator to make sure all the necessary arrangements are done at the site.

The shipping and receiving staff should then deliver only the cases to the specific clinic/department. Always alert the shipping and receiving group at your site and make sure there is a system in place to deliver the formula to you. The shrink wrapping and pallet is to prevent denting of the cans or damaging the boxes with labels/dirt.

It is recommended to stack each color in separate groups so you can easily pull for participants. For example you could have 2 stacks of 5 cases of one randomization color: 40 " high x 14" wide x 10 5/8 " deep. And arrange 4 columns of each color in your storage space.

The smallest number of cases that can be ordered of each color is 10. We expect sites to be ordering from Eminent every week or every 2 weeks for this study for formula. If you know you will have more than one Entry B infant coming to an Infant Enrollment visit, please order an additional 10 boxes of each color multiplied by # of participants since you do not know which color they will be randomized to. You will need to order right after the visit (once you know each participant's randomization color) so that the participant has enough formula until the next visit. The participant should at least carry with them 3 cases of formula from the clinic visit. (Each formula box contains 6 x 32 oz cans. This should feed one infant for a 6 days.) If you order right after the Infant Enrollment visit, the formula should be delivered to your site in 2 weeks. Then you would need to arrange a courier to deliver the rest of the formula required until the next visit (or have the participant come by the clinic to pick it up).

2.7. Accountability

In order to comply with FDA regulations, each site is required to keep a record of receipts and dispositions of all study substance received from EMINENT. *Investigational Study Substance Accountability* forms for formula and capsules, respectively, are provided for this use. This form can be found on the TrialNet website under NIP/Resources/View all study documents/ Essential Documents Binder. There one form for capsules and one form for formula.

When study substances are returned to the site, please note the date of return directly on the bottle or can using a permanent marker (Magic Marker® or Sharpie® type implements). Study substance is NOT returned to stock for re-dispensation.

2.8. Returning Study Medication

Study substances, both used and unused, shall be returned to EMINENT for the following reasons:

- The study is completed or terminated,
- The study substance has expired,
- The study substance has been stored improperly or was received damaged
- The study substance return was requested by the EMINENT pharmacist, and/or

- A participant returns study substance to the site

NOTE: The study substances are not to be returned to site stock once it has been dispensed to a subject.

A copy of the *Study Agent Return Form* is located on the TrialNet Website under NIP/Resources/View all study documents/Essential Documents Binder/TN06 Study Agent Return Form. This is a specific form for the NIP trial. The following are instructions on how to fill out a Study Agent Return Form.

Instructions for Returning Study Supplies to EMINENT

1. Complete all sections of the form, except the right-hand section with the heading FOR EMINENT USE ONLY (shaded area).
2. *Agent Return Form – Formula* for formula only. *Agent Return Form- Capsules* for capsules only.
2. Print site address on the form.
3. Quantity: Enter the total number of dosage units (cans of formula or number of capsules) being returned.
6. Sign and date the form. Please include the site phone number.
8. Enclose ONLY those items that EMINENT provided.
9. Include the completed *Agent Return Form* in the package. Make a copy of the completed form for your records.
10. *Pack the materials so that they will not be damaged during transit!* Ship all items at room temperature.
11. The EMINENT address is located in the upper right of the *Agent Return Form*.
12. Return to EMINENT via traceable courier (FED EX, UPS, etc) and retain a copy of the air bill for tracking purposes.

2.9. Unmasking Treatment Group Assignment

In the event that the treatment group assignment of a participant needs to be unmasked, The Coordinating Center must be contacted.

CHAPTER 11 STUDY SUBSTANCE DISPENSATION AND ADMINISTRATION

1. Modes of Administering DHA or Placebo

The infant will receive study substance either by breastfeeding (mother will take capsules), taking study formula, and/or by consuming the contents of study capsules that have been mixed in with infant's solid food. A combination of these modes will take place in the event the mother is partially breastfeeding and/or when the infant reaches 6 months of age.

2. Study Substance Procedures

The distribution of study substance will depend on if the mother is going to breastfeed the baby or not.

2. 1 ENTRY A Study Substance Procedures:

Pregnant Woman Screening/Enrollment Visit

- No Nursing mothers

If a pregnant woman does not plan to breastfeed, give her 3 cases of study formula and ship 2 additional cases so they arrive at her home approximately 2 weeks after the birth of the infant. The formula should last until she comes for the Entry A Infant Screening Visit 2-28 days after delivery. One case of stud formula will last approximately 1 week. Do not dispense capsules.

- Nursing mothers

Mothers who plan to breastfeed will be given enough study capsules to last until they come for the Entry A Infant Screening Visit. The calculations below have been done as if all mothers will deliver at 42 weeks, therefore mothers enrolling at 24 weeks will need a 22 week supply of capsules. That means that she will need to be given 7 bottles of capsules. The capsule distributions for women to enter later than 24 weeks are listed below.

Note: Nursing mothers will also be given one case of study formula in case they have trouble breastfeeding, or decide not to breastfeed for other reasons.

Week of Pregnancy at the Screening and Enrollment Visit	Number of Bottles of Study Capsules to Give the Mother
24 weeks	7 bottles
25 weeks to 28 weeks	6 bottles
29 weeks to 31 weeks	5 bottles
32 weeks to 35 weeks	4 bottles
36 weeks to 38 weeks	3 bottles
39 weeks to 42 weeks	2 bottles

The first dose should be given during the clinic visit (4 capsules/day).

Entry A Infant Screening Visit (2-28 days after birth)

Give study substance (capsules or formula) sufficient to last until the Infant Enrollment Visit approximately 4 weeks later.

- No Nursing mothers

If the mother is still using study formula, consider what stock of study formula the mother might have at home. Take into account that she will need about a case for each week. She should have at least 4-5 cases on hand to last until next visit. Dispense 3-4 cases initially and periodically send the rest to the participant's home in the same 3-4 case increments.

> Some infants may not tolerate the study formula, but the parents may wish to remain in the study. We encourage them to continue participation and recommend that they hold off on study substance until capsules can be mixed into the infant's food at 6 months of age.

- Nursing mothers

If she plans to breastfeed, the mother should be given 2 bottles of capsules (200 capsules). She should also be given one case of formula in the event she has difficulty breastfeeding.

Entry A Infant Enrollment Visit (4 weeks after HLA blood collection)

The infant will be approximately 4-8 weeks old at the Infant Enrollment Visit, and will attend the 3 Month Follow-up Visit between 2 ½ to 3 ½ months of age (2 week window on either side of the visit age). Give a supply of study substance that will last until the 3 Month Follow-up visit.

- No Nursing mothers

The study formula dispensed at this point will be highly dependant on the age of the infant at this time. Estimate the **number of weeks** from the time of the Infant Enrollment Visit to the time of the 3 Month Follow-up Visit and plan to give the mother at least 1 case of formula for each week. Two to three cases should be sent to the participant's home by FedEx or courier every two weeks to maintain control over your site's supplies.

- Nursing mothers

The study capsules dispensed at this point will be highly dependant on the amount of time that will elapse before the next visit. Estimate the **number of days** from the time of the Infant Enrollment Visit to the time of the 3 Month Follow-up Visit and give the mother at least 1bottle of study capsules for every 25 days that will elapse before the participant will return to the site. For a 3 moth supply, dispense 4 bottles of study capsules. She should also be given one case of formula in the event she has difficulty breastfeeding.

Three month Old visit

- No Nursing mothers

Participants who are continuing in the study will be given study formula again (1case per week). Dispense 3-4 cases initially to the mother and periodically mail the rest to the participant's home in the same 3-4 case increments.

- Nursing mothers

When the mother comes for the 3 month visit, and if she is still breastfeeding, give 4 bottles of study capsules for a 3 month supply. She should also be given one case of formula in the event she has difficulty breastfeeding.

Six month Old Visit/ 9 Month Visit

- No Nursing mothers

Participants who are continuing in the study will be given study formula again (1case per week). Dispense 3-4 cases initially to the mother and periodically mail the rest to the participant's home in the same 3-4 case increments. It is assumed that infants will start eating solid foods from this time on. Formula dispensation will vary after 6 months of age since capsules will be mixed into the infant's **solid** food according to the amount of study formula he or she is taking.

Amount of formula/day	**Number of capsules mixed with infant's solid food/day**
≤ 16oz study formula per day	2 study capsules
16 to 32oz per day	1 study capsule
at least 32oz per day	No capsules added

The administration of study formula will continue in the same fashion as the six month visit until the infant reaches 12 months of age.

- Nursing mothers

She will be given 4 bottles of capsules at each of the 6 and 9 month visits. For as long as the mother is breastfeeding, she will continue to take 4 study capsules per day, but will supplement the child's diet with study formula (if less than 6 months of age) or contents of capsules (if older than 6 months of age and taking sols foods).

If the infant is partially breastfeeding and not yet tasting solid foods at 6 months of age, it is acceptable to wait on giving a capsule each day, as it will not mix well into liquids. The mother should continue taking 4 caps each day and will mix a capsule into the infant's solid food when he or she begins to try solid foods. A capsule should be mixed into the food on any

days when the infant tastes solid foods. It is understood that at first the infant may not necessarily eat each day, and that the capsule mixing will slowly be incorporated over time.

12 Month Old Follow-up to 36 Months

- No Nursing mothers

No study formula will be provided after 12 months of age; however the participant may choose to purchase formula if they wish. The participant must ensure that the purchased formula supplemented with DHA. The contents of two study capsules will be mixed into the infant's solid food each day. From 12 months to 36 months of age, participants should be given 3 bottles of capsules at each follow up visit to last until the next.

- Nursing mothers

Mothers will not breastfeed or take study capsules after the baby is 12 months old. Instead, the contents of two capsules will be mixed into the infant's solid food each day. From 12 months to 36 months of age, participants should be given 3 bottles of capsules at each Follow-up Visit to last until their next Follow-up Visit.

36 Month Old Follow-up

No study capsules will be dispensed or taken after the 36 months of age visit. Participants should return all full and empty study substance containers to this visit.

2. 2 Entry B Study Substance Procedures:

Entry B Infant Screening Visit (2 days to 5 months of age)

No study substance (capsules or formula) will be given until after the HLA is known and the infant is enrolled and randomized into the study.

Infant Enrollment Visit (4 weeks after HLA collection)

The amount of study product will depend on when is going to be the next Follow-up visit. If the infant is screened at or before two months of age, their next Follow-up visit will likely be the 3 Month Follow-up Visit. If the infant is screened after two months of age, their first follow up visit will likely be at 6 months, since visits are scheduled by age, not by the length of time in the study. If the infant is within the two week visit windows of the 3 or 6 Month Old Follow-up Visit, the Infant Enrollment and Follow-up Visit may be combined. Details on this combined visit can be found on the NCL06 Entry B Infant Enrollment Visit Checklist.

- No Nursing mothers

The amount of study formula dispensed at this point will be highly dependant on the age of the infant at this time.

When scheduling the next logical follow up visit (3 or 6 Month Follow-up), estimate the number of weeks between the visits and give at least 1 case of formula for each week that will elapse before the participant will return to the site. Dispense 3-4 cases initially and periodically send the rest to the participant's home in the same 3-4 case increments.

- Nursing mothers

The amount of study capsules dispensed at this point will be highly dependant on the age of the infant at this time. Estimate the number of days between visits and give at least 1 bottle of capsules for every 25 days that will elapse before the participant will return to the site. If it's going to be a 3 month supply, dispense 4 bottles of study capsule. She should also be given one case of formula in the event she has difficulty breastfeeding.

3 Month Old follow-up

- No Nursing mothers

When scheduling the next logical follow up visit, give at least 1 case of formula for each week that will elapse before the participant will return to the site. Dispense 3-4 cases initially and periodically send the rest to the participant's home in the same 3-4 case increments.

Some infants may not tolerate the study formula, but the parents may wish to remain in the study. We encourage them to continue participation and recommend that they hold off on study substance until capsules can be mixed into the infant's food at 6 months of age.

- Nursing mothers

When the mother comes for the 3 month visit, and if she is still breastfeeding, give 4 bottles of study capsules. She should also be given one case of formula in the event she has difficulty breastfeeding.

6 Month Old Follow-up

- No Nursing mothers

Formula dispensation will vary after 6 months of age because at this point capsules will be mixed into the infant's solid food according to the amount of study formula he or she is taking.

Amount of formula/day	**Number of capsules mixed with infant's solid food/day**
≤ 16oz study formula per day	2 study capsules
16 to 32oz per day	1 study capsule
at least 32oz per day	No capsules added

- Nursing mothers

She will be given 4 bottles of capsules at each of the 6 and 9 month visits. If the mother partially stops breastfeeding before one year of age, she will continue to take 4 study capsules per day, but will supplement the child's diet with study formula (if less than 6 months of age) or contents of capsules (if older than 6 months of age and taking sols foods). If the infant is partially breastfeeding and not yet tasting solid foods at 6 months of age, it is acceptable to wait on giving a capsule each day, as it will not mix well into liquids. The mother should

continue taking 4 caps each day and will mix a capsule into the infant's food when he or she begins to try solid foods. A capsule should be mixed into the food on any days when the infant tastes solid foods. It is understood that at first the infant may not necessarily eat each day, and that the capsule mixing will slowly be incorporated over time.

9 Month Old Follow-up

- No Nursing mothers

The administration of study formula will continue in the same fashion as the 6 Month Follow-up until the infant reaches 12 months of age.

- Nursing mothers

The administration of study capsules will remain the same as the 6 Month Follow-up until the infant reaches 12 months of age.

12 Month Old Follow-up to 36 Months

- No Nursing mothers

No formula will be given after 12 months of age. Instead, the contents of two capsules will be mixed into the infant's food each day. From 12 months to 36 months of age, participants should be given 3 bottles of capsules at each Follow-up visit to last until their next Follow-up visit.

- Nursing mothers

Mothers will not breastfeed or take study capsules after the baby is 12 months old. Instead, the contents of two capsules will be mixed into the infant's food each day. From 12 months to 36 months of age, participants should be given 3 bottles of capsules at each Follow-up Visit to last until their next Follow-up Visit.

36 Month Old Follow-up

No study capsules will be dispensed or taken after the 36 Months of Age Visit. Participants should return all full and empty study substance containers to this visit.

a. **Dispensing the Study Formula**

Unopened formula should be stored at room temperature in a cool, dry place until cans are needed. Clean the top of the can, shake well, and then open. Divide can content among bottles and refrigerate the bottles. The bottles are good for up to 48 hours as long as they are sealed and refrigerated. Dispose of any open cans of formula that have been at room temperature for an hour or more. If the infant begins to drink a bottle of formula and does not finish it, throw away the remaining contents of the bottle.

Participants should bring any unused study capsules as well as empty bottles back to the site with them at each visit. Each site must account for returned study substances, keep separate from the regular stock, and send these materials back to Eminent for destruction.

If at any point an infant is partially breastfeeding and partially taking solid foods, they should be treated as if they are exclusively nursing and exclusively mixing capsules into their food.

Summary of Study Substance Intake for Mother and Baby

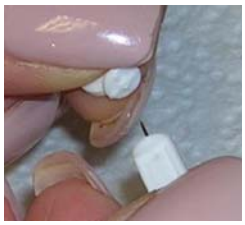
	Baby's Age				
	3rd trimester to Birth	**Birth to 4 mos**	**4 to 6 mos**	**6 to 12 mos**	**12 to 36 months of age or end of study**
Mother					
Pregnant (if nursing)	4 caps/day	NA	NA	NA	NA
Exclusively nursing	NA	4 caps/day	4 caps/day	4 caps/day	0
Partially nursing and providing study formula	NA	4 caps/day	4 caps/day	4 caps/day	0
Baby					
Nursing	NA	0	0	1 cap/day	2 caps/day
Partially nursing and taking study formula or Exclusively taking study formula	NA	Study Formula	Study Formula	32 oz of Study Formula or 16 to 32 oz of Study Formula plus 1 cap/day or ≤16 oz of Study Formula plus 2 cap/day	2 caps/day

3. How to mix the capsule content with baby's food

The NIP Diabetes study substance is a football shaped capsule and is filled with liquid oil. Softclix® lancets will be supplied to participants for puncturing the study capsules (see below). One lancet may be used to puncture any number of necessary capsules for one day. For safety purposes, instruct participants to recap the lancet after each use and keep in a safe place. At the end of the day, the participant is to safely discard the re-capped lancets. Please note that the Softclix® lancets are not to be used in a lanceting device.

Instructions for puncturing study capsules

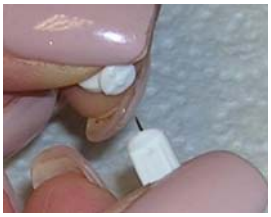
When demonstrating to the mother how to puncture the capsules, DO NOT USE a study capsule. ONLY use vitamin D provided for this demonstration.

1.  Remove the Accu-Chek™ Softclix® lancet cap off the lancet. Do NOT use a lancet that has punctured human skin. Do NOT place the lancet in an auto-lanceting device.

2.  Place the capsule between your thumb and finger(s) of one hand with the pointed end of the "football" facing away from your fingers.

3.  Hold the capsule in this position with minimal pressure (CAUTION: too much pressure will cause the oil to squirt from the capsule). Place the lancet between your thumb and forefinger of your other hand, with the sharp end pointed away from your fingers. Gently puncture the pointed end of the capsule.

4.  Point the punctured end of the capsule toward the food that you wish to mix with the oil. Gently squeeze the capsule until all of the oil is expressed. Check the capsule for any remaining oil. If oil remains in the capsule, squeeze into the food a second time with increased pressure.

5.  Recap the lancet carefully and discard or keep for future reuse.

Keep the lancet in a clean and dry place if it is to be reused. Do NOT use the same lancet for more than one day to puncture study capsules. Do NOT use an old lancet the next day to puncture the study substance capsule.

Discard the remaining squeezed capsule casing into your trash can.

Tips for Mixing Study Capsule Contents Into Food

1	Mix the contents from the study capsule into a spoonful of food so your baby will take the entire dose.
2	Do not cook or heat the oil from the study capsule.
3	Consider mixing the oil of the study capsule with rice cereal, oatmeal, pureed fruits, and/or pureed vegetables. You will need to find what works best for your child
4	If your baby spits up the study substance, don't worry. Just start again with the next scheduled dose and keep giving the rest of the doses as you normally would

4. Participant Study Substance Compliance and Vacations

Due to the duration of the study and the possibility of parents going on vacation during the holidays, these are some guidelines to be followed. Always take into account the amount of time parents will be on vacation and the mailing time.

<u>Enrolled participants only taking study formula and not able to take any solid foods:</u>

- *Traveling on vacation to a single North America destination and can ship to location:*

Parents should travel with a few study formula cans. Site Coordinator ships the rest of the study formula to the vacation destination. Site must follow-up with the parents to ensure that all of the study formula cans arrived in good condition.

- *Traveling on vacation to multiple destinations or to a location where shipping is not an option:*

Parents are advised to purchase Enfamil Lipil with Iron (any form) off the shelf. They will not be reimbursed for purchasing this suggested formula. Note if the participant was assigned to the experimental treatment group (higher DHA), levels will return to baseline in 4 weeks without continued intake, so it is important that this non-compliance alternative be as brief as possible.

Complete the following forms:

- **NPP16 Study Substance Compliance Form** to indicate the participant's non-compliance at the next scheduled visit.
- **NPP19 Protocol Deviation Form** because the participant is independently taking DHA/omega 3 fatty acid supplement; you may note the approval of this action by the NIP Diabetes Pilot Advisory Group **if the above is followed and limited to two weeks**.

Enrolled participants, younger than 6 months of age, taking study formula and solid foods:

- *Traveling on vacation to a single North America destination and can ship to location:*

The study formula is the preferred method of delivery of the study substance. Parents should travel with a few cans. Site Coordinator ships the rest of the study formula to the vacation destination. Site must follow-up with the parents to ensure that all of the study formula cans arrived in good condition.

- *Traveling on vacation to multiple destinations or to a location where shipping is not an option:*

The study formula is the preferred method of delivery of the study substance. When infants are just being introduced to foods, it is difficult for solid food to be taken into the participant's

system (e.g. tends to be spit out). As a temporary option to study formula while the participant is on vacation, the recommended action is for the parent to mix the contents of 2 study capsules into a teaspoon of food.

Complete the following forms:

- **NPP15 Study Substance Dispensation and Return Form** to dispense study capsules and change the prescription. This is to be completed and submitted at the time of the dose change.
- **NPP16 Study Substance Compliance Form** to indicate the participant's level of compliance at the next scheduled visit.
- **NPP19 Protocol Deviation Form** because the less than 6 months age participant is taking the study substance in a form not approved by the current protocol. You may note the approval of this action by the NIP Diabetes Pilot Advisory Group **if the above is followed and limited to two weeks**.

Shipping of Study Formula during Hot Weather:

1. Pack as under regular circumstances.
2. All study formula should be FedEx Overnight such that the formula is not left in high temperatures.
3. Keep in mind FedEx holidays and weekend delivery times and the participant's availability for receiving the study formula.
4. Note any issues on the **NPP15 Study Substance Dispensation and Return Form**.

Shipping of Study Capsules during Hot Weather:

1. Pack the study gel capsules in a sealed waterproof bag and surround with refrigerated cold ice packs.
2. Place in a Styrofoam shipper and notify the participant's family of the package (and how it is packed).
3. Ship FedEx Overnight.
4. Keep in mind FedEx holidays and weekend delivery times and the participant's availability for receiving the study capsules.

5. Note any issues on the **NPP15 Study Substance Dispensation and Return Form**.

During the hot weather, recommend participant carry only the amount needed for the day/week in a pill box and the rest remain at home.

CHAPTER 12 PARTICIPANT STATUS

1. Changing Study Status

If a participant chooses to be inactive for any reason, they should be encouraged to continue/restart supplementation with study substance and should be encouraged to attend follow-up visits.

1.1. Inactive Status

In the event that a participant is unable or unwilling to continue making future visits then the participant is declared inactive. Every effort should be made to encourage all participants to continue making follow-up visits. If a participant is declared inactive, the Participant Status Form (**NPP18**) must be completed.

1.2. Reactivation into the Study

In some circumstances, a participant may enter inactive status and be unwilling or unable to return to the study clinic for future visits. It is hoped that at a later date this participant may decide to once again resume active participation in the study. If the participant desires to return to the clinic for future follow-up visits, he/she should be allowed and encouraged to do so. The participant should be allowed to return to active participation regardless of the length of the inactivity period, as long as the study is still active. If a participant who is inactive decides to become reactivated, the Participant Status Form (**NPP18**) must be completed.

This form is completed for *every* change of status that occurs. Therefore, if a participant becomes inactive and then reactivates at a later date, two separate forms should be completed. Completion of this form allows The Coordinating Center and the clinical site to document and track that a participant is no longer actively participating in the study and, therefore, not to expect any forms or other information. Conversely, if a participant is becoming active again following a period of inactivity, the completion of this form allows The Coordinating Center and the clinical site to document and track that a participant is once again participating in the study and to begin expecting forms and other information from that participant according to the study schedule.

CHAPTER 13 REPORTS

1. Infant Eligibility Reports (Example in Appendix H)

1. The TrialNet Coordinating Center will post the Infant Eligibility Report for each participating site to the secure TrialNet website. An automatic email will be generated to inform the primary Site Coordinator for this study when it is posted.
2. Occasionally the Infant Eligibility Report will be emailed directly to the primary Site Coordinator for this study.
3. Only certified site staff will have access to site-specific reports on the secure TrialNet website.
4. One Adobe .pdf file will contain all Infant Eligibility Reports for the site.
5. Participant families should not view or have a copy of the Infant Eligibility Report. Select information may be conveyed to the participant's family. See *Information That May Be Disclosed to the Participant's Family* below.
6. The following data must be available at TrialNet Coordinating Center to generate the report: NPP01 General Screening Form, NPP04 Infant Screening Form, NIP99IHL and the CHORI HLA lab results.
7. Infant Eligibility Report is described as follows:

   - **HEADER:** Contains unique identifying participant information and the date of the Infant Screening visit.

   - **SECTION 1**: **PARTICIPANT INFORMATION:** Section 1 contains information about the participant (infant) as collected on the NPP04 form. If date of birth is missing or has been flagged as an edit, then related fields will have missing information in this section until the edit has been received and keyed at TNCC. The last date the eligible infant must be randomized to participate in the study is calculated as the date of birth + 182 days.

   - **SECTION 2**: **LAB RESULTS:** Section 2 reports when the HLA specimen was collected and the higher or lower risk status of the HLA type (based on absence/presence of DR3, DR4, and protective HLA alleles).

- **SECTION 3**: **BIOLOGICAL FAMILY HISTORY INFORMATION:** Section 3 contains information as collected on the NPP01 form. If the participant's family history has changed from the date the form was completed, you will need to send an edit to TNCC so this can be accurately reflected in the report. Family history of type 1 diabetes will be important in determining eligibility if the HLA risk is "lower risk".

- **Eligible based on HLA and T1D Family History**: If the report indicates "No", then the infant is not eligible based on the HLA and T1D family history. If the report indicates "Yes" and Entry B infant, confirm that the other eligibility criteria are met per protocol. At this point the infant can be randomized. If the report indicates "Yes" and Entry A infant, confirm that the other eligibility criteria are met per protocol on the NPP25 Entry A: Verification of Infant Eligibility Form and assigned the same treatment as the mother's.

- **Possible Reporting Scenarios:** Below are a number of Infant Eligibility Report result scenarios that require interpretation by the site coordinator to convey protocol-approved information to the participant's family.

SCENARIO SUMMARY TABLE

Scenario	HLA Risk	T1D Family History	The only information that may be disclosed to the Participant's Family:
1	Lower risk	Has only one 1st degree relative	Lower risk to develop T1D than those who qualify for this study – Not eligible
2	Lower risk	Has only 2nd degree relatives	Lower risk to develop T1D than those who qualify for this study – Not eligible
3	Lower risk	2 or more x 1st degree relative OR 1 x 1st deg relative 1 or more x 2nd deg relative	Higher risk to develop T1D – **Eligible**
4	Higher risk	1 or more x 1st degree relative 0 or more x 2nd degree relative	Higher risk to develop T1D – **Eligible**

CHAPTER 14 ASSESSMENT AND MANAGEMENT OF ADVERSE EVENTS

1. Definition

Per ICH guidelines for Good Clinical Practice, an **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical produce and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medical (investigational) product, whether or not related to the medicinal (investigational) product. Adverse events include, but are not limited to the following:

- A worsening or change in nature, severity, or frequency of conditions present at the start of the study;
- Participant deterioration due to primary illness;
- Intercurrent illness; and
- Drug interaction.

Participants should be questioned at each scheduled visit in a general way, without asking about the occurrence of any specific symptom. The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the adverse event and not the individual signs or symptoms.

Following questioning and evaluation, all adverse events, whether believed by the investigator to be related or unrelated to the study drug, must be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the Adverse Event Report Form. Each adverse event is to be evaluated for duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the study drug. An adverse event is determined to be associated with the use of the study drug "if there is a reasonable possibility that the AE may have been caused by the drug". (21 CFR 312.32 [a]). It should be

noted that the term "severe" used to grade intensity is not synonymous with the term "serious."

Adverse events do not include the following:

- Continuous persistent disease/symptom present before study start, which does not unexpectedly progress, or change in severity
- Disease being studied or signs/symptoms associated with the disease.
- Symptoms of desired pharmacological effect
- Treatment failure or lack of efficacy.

2. Intensity of Adverse Events

All adverse events must be graded for intensity. Each adverse event will be graded based on the National Cancer Institute's Common Terminology Criteria for Adverse Events v3.0 (December 12, 2003). An intensity grade between 1 and 5, as defined in the following table, must be entered on the Adverse Event Report Form.

Grade	Description
1	A mild adverse event. A symptom that may be an annoyance but does not interfere with the participant's usual function. Or Requires no intervention
2	A moderate adverse event. A symptom that impairs the participant's usual function, but presents no danger to the participant. Or Resolves with minimal, non-invasive intervention.
3	A severe adverse event resulting in hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
4	A life-threatening or disabling adverse event
5	A fatal adverse event

3. Relationship to Study Drug

The investigator will document his/her opinion of the relationship of the adverse event to the study medication using the criteria outlined in the following table. This relationship should be recorded on the Adverse Event Report Form (NPP23).

Grade	Description
Not related (0% chance)	This category is applicable to those adverse events that are clearly due to extraneous causes (concurrent drugs, environment, etc.) and are not related in any way to the study medication (0% chance)
Unlikely (1 – 19% chance)	An adverse may be considered unlikely to be related if (must have the first two): a) It does not occur within a reasonable time following administration of the test article. b) It could readily have been produced by the participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant. c) It does not follow a known response pattern to the suspected drug. d) It does not reappear or worsen when the test article is re-administered.
Possible (20-50% CHANCE)	An adverse event may be considered possibly related if (must have the first two): a) It occurs within a reasonable time following administration of the test article. b) It could have been produced by the participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant. c) It follows a known response pattern to the suspected drug.

Probable (51 – 99% chance)	An adverse event may be considered probably related if (must have the first three): a) It occurs within a reasonable time following administration of test article. b) It could not be reasonably explained by the known characteristics of the participant's clinical state, environmental or toxic factors or other modes of therapy administered to the participant. c) It disappears or decreases on cessation or reduction in drug dose. There are exceptions when an AE may not disappear upon discontinuation of the drug (e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc.) d) It follows a known response pattern to the suspected drug.
Definitely (100% chance)	An adverse event may be considered definitely related if (must have the first four): a) It occurs within a reasonable time following administration of the test article. b) It could not be reasonably explained by the known characteristics of the participant's clinical state, environmental or toxic factors or other modes of therapy administered to the participant. c) It disappears or decreases on cessation or reduction in drug dose. There are exceptions when an AE may not disappear upon discontinuation of the drug (e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc.) d) It follows a known response pattern to the suspected drug. e) It reappears or worsens when the drug is re-

	administered.

4. Reporting Adverse Events

All adverse events independently of the intensity must be recorded on the Source Documents, however only all adverse events with intensity of **grade 2 or above** will be recorded on the adverse event report form (NPP23) and send to the TrialNet Coordinating Center.

All adverse events that are UNEXPECTED or SERIOUS in nature should be reported.

An **unexpected adverse** event is defined as one for which the specificity or severity is not consistent with the current Investigator's Brochure.

Events that are an **expected risk** of the research, but **serious** in nature should be **reported**. This would include those events for which the **participant sought treatment**, **went to the ER** or was **admitted to the hospital** or **resulted in death**.

The NPP23 form is completed for any adverse events with intensity of grade 2 or more (either reported or observed) for pregnant woman or infant, whether serious or non-serious, as well as any changes in intensity, frequency, or duration of a previously reported adverse event, even if the adverse event is the same.

- For nursing mother, adverse events need to be collected for the mother and the baby.
- For non-nursing mothers, collected adverse events only for the baby
- For Entry A babies, any infant delivery problems should be reported as adverse events

Each adverse event will require the completion of a **separate** Adverse Event Report Form (NPP23). The investigator will provide information on the dates of onset and resolution (if

known), intensity, seriousness, frequency, action(s) taken, relationship to study drug, and outcome.

A new Adverse Event Report Form (NPP23) will be completed to document any changes in the intensity or seriousness of an adverse event, even if the event is the same.

4.1. Immediately Reportable Events

The following categories of medical events that could occur during participation in this study must be reported to the **Coordinating Center** within **24-hours** of first knowledge of the event:

- Serious Adverse Event (SAE)
- Pregnancy
- Treatment unmasking for any reason

5. Management of Adverse Events

All adverse events will be documented on the adverse events data collection forms, will be managed by the diabetologists and clinical staff at the study clinics, and will be monitored by the Data Safety Monitoring Board. If a participant dies at any point during the study, the death will be reported to the Data Safety Monitoring Board and investigated.

6. Serious Adverse Events

An adverse event is deemed serious if it results in any of the following outcomes:

- Death.
- A life-threatening experience. Life-threatening means that the participant was in the view of the investigator, at immediate risk of death from the reaction as it occurred.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalization for elective treatment or a pre-existing condition that did not worsen during the clinical investigation is not considered an adverse event. Hospitalization or nursing home admission for the purpose of caregiver respite is not considered an adverse

event. Complications that occur during hospitalization are adverse events, and if a complication prolongs hospitalization, the adverse event is considered serious. Treatment in a hospital emergency room is not a hospitalization. It is the fact of being admitted to the hospital, which meets these criteria, not the duration of hospital stay.

- Results in a persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly or birth defect in the offspring of a participant (only if the offspring was exposed to the investigational product in utero).
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious adverse events when they may jeopardize the health of the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Any other event thought by the investigator to be serious should also be reported, following the reporting requirements detailed in this section. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization.

6.1. Management of Serious Adverse Events

A physician will examine participants experiencing a serious adverse event or an emergency situation as soon as possible. The physician in attendance will do whatever is medically needed for the safety and well being of the participant. The participant will remain under observation as long as medically indicated. Appropriate laboratory studies will be conducted until all parameters return to normal or are otherwise explained or stable. The participant will be followed until the serious adverse event resolves or until the participant is medically stabilized. The Principal Investigator or delegate will notify the Coordinating Center (and the Research Ethics Committee, if necessary) immediately of the serious adverse event and the outcome of the serious adverse event.

6.2. Reporting Serious Adverse Events

Any Serious Adverse Event needs to be reported to the **Coordinating Center** within **24-hours** of first knowledge of the event. Two reports must be sent :

- The Adverse Event Report Form (NPP23) must be completed with as much information as is known at the time and faxed to the Coordinating Center at the following fax number:

  Fax: (301) 468-1676 OR (866) 804-6058

  Tel: (301) 881-9260

- The TrialNet MedWatch Form (RITSA) must be completed with as much information as is known at the time and faxed to the Coordinating Center at the following fax number:

  Fax: (301) 468-1676 OR (866) 804-6058

This form that will be reviewed by the TrialNet Medical Monitor. The Medical Monitor will determine if the event qualifies to be reported to the FDA. The Medical Monitor will call the study site to confirm that he has received the TrialNet MedWatch Form within **24 hours** of the time the form was initially faxed. If you do not receive this confirmatory call within 24 hours of faxing the form, the MedWatch Form **must be re-faxed to the number indicated above.** In addition, the Medical Monitor may contact the study site to request further information that may be useful in determining the need to report the event to the FDA.

7. Post-Study Follow-Up of Adverse Events

All adverse events, including clinically significant adverse changes in clinical status or physical examination findings, must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the participant is lost to follow-up. If resolved, a resolution date should be documented on an update of the original Adverse Event Report Form (NPP23). Adverse events ongoing at the final visit or at early termination will be followed for as long as necessary to adequately evaluate the participant's safety or until the event stabilizes or resolves or until the participant is lost to follow-up. The investigator is responsible for

ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the adverse event. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals, as is practical.

8. Unmasking

The study substance will be color coded using four different colors in order to preserve the study blinding. Subjects will be informed that they will be receiving either the study substance or a control during the course of the study. Once a subject has been randomized, the investigator, the subject, parents or guardians, as well as all staff involved in the conduct or management of the study will be blinded to the subject's treatment assignment.

In the event of an adverse event or other circumstance requiring unblinding, the Principal Investigator will contact the Coordinating Center within 24 hours of the event. The TrialNet Central Pharmacy will maintain a list of each participant's group assignment, and it will be able to unmask a participant's treatment group assignment. In the case of a serious adverse event or any adverse event, TrialNet research personnel will not be unmasked unless it is essential to know the study group in order to treat the participant.

Unmasking (normal business hours): (240) 629-1972

24-hour Emergency Hotline: (888) 321-4364

If TrialNet research personnel are unmasked about a given study participant's treatment group assignment, the participant will still be encouraged to continue with the schedule of follow-up assessments.

Expectedness should be assessed using the Investigator's Brochures (IB) and the locally approved labeling. The investigator must record the reason for breaking the blind in the subject's source documents. Participants will be encourage to share this information with her

obstetric care provider or pediatrician. If the participant so desires, study staff may directly contact her obstetric care provider regarding these issues.

CHAPTER 15 PROTOCOL ADHERENCE

This section contains specific information about participant protocol adherence requirements. This includes information on expected adherence to the visit schedule as well as the study medication. The section also includes the details of specific protocol deviations and actions that need to be taken to address these deviations.

1. Protocol Deviations

This section provides specific examples of protocol deviations and what actions need to be taken to address these deviations. Every effort should be made to ensure that no protocol deviations occur. If any deviations do occur, the Protocol Deviations Form (**NPP19**) needs to be completed.

Examples of Protocol Deviations

The following list (not meant to be exhaustive) provides examples of other protocol deviations that would require the completion of the Protocol Deviation Form (NPP19):

- Randomization of an ineligible subject
- Study substance error (i.e. incorrect dose)
- Capsules given prior to 6 month of age
- Infant fed non-study formula containing DHA
- Vitamin E capsules given instead of Study Substance capsules
- Entry A infant screening conducted outside of visit window (> 28 days after birth)
- Sample collection schedule specified in the protocol not followed

CHAPTER 16 FORM COMPLETION

1. Form Shipment

All study forms completed at the participating clinical centers will be mailed to the Coordinating Center for entry into the official database. These forms should be mailed using the FedEx PassKey System to the following address:

Type 1 Diabetes TrialNet Coordinating Center
The GWU Biostatistics Center
6110 Executive Blvd., Suite 500
Rockville, MD 20852
Contact: FORMS Seshu Pakalapti
Phone: (301) 881-9260
Fax: (301) 881-0179

A mailing list should be included with **ALL** shipments of forms. This should be an annotated list of all the forms included in the mailing. Once a particular mailing is received by the Coordinating Center, this mailing list is checked to ensure that all the indicated forms are included. Each of the received forms is stamped with the date of receipt at the Coordinating Center.

2. Instructions for Completing Forms

These instructions provide assistance for completing the study forms pages for this study. Although these guidelines do provide direction, they cannot address every situation. **If in doubt about the correct way to complete any section of the CRF, please call the Research Assistant or the Protocol manager at TrialNet Coordinating Center.**

For all entries:

- Use a BLACK or BLUE ballpoint pen and press firmly when completing the CRFs. Do **not** use pencil.
- All entries must be legible and printed clearly (press firmly to ensure all copies are clear).
- Attention to correct spelling and accurate information is important.
- All entries are marked with a "✓" or an "X" in applicable boxes.

If a correction must be made:

- **Never** use "white-out" or erase an original entry.
- Draw a **single line** through the error
- Re-enter the correct data near the original entry, and initial and date the correction **(all changes must be initialed and dated by study personnel).**
- Record the correct information close to the original entry (do **not** write over the previous entry)

Answer every question. Leave no spaces or boxes blank unless otherwise specified. If necessary, use the missing value codes:

- **"*" –** The asterisk indicates that the value is permanently missing or
- **"?" -** The question mark indicates that the value is currently unavailable.

In the case of twins, complete mother study forms (CRFs and STFs) only ONCE, but complete separate CRFs and STFs for each child.

When boxes are provided for entering data, enter one character per box.

Do not use abbreviations.

The site must retain all original source documents in a separate individual subject file. Data on source documents will be checked and compared to data on the CRFs. Source documents and raw data used to complete the CRFs (hospital and clinic charts, office files, appointment records, etc.) must be available and accessible for review during the site monitoring visits.

Dates should be recorded using the DAY/MONTH/YEAR format, which utilizes two-digits for the date, three-characters for the month, and four-digits for the year. Indicate the month as three-characters (e.g., Sep for September). Indicate the year as four-digits (e.g., 1972 instead of 72). Use the key below for the months:

January	= JAN	February	= FEB	March	= MAR	April	= APR
May	= MAY	June	= JUN	July	= JUL	August	= AUG
September	= SEP	October	= OCT	November	= NOV	December	= DEC

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

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

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

***** If the 12-hour time is midnight (12:00 am), please record this in 24-hour format **00:00** on the **next** day.

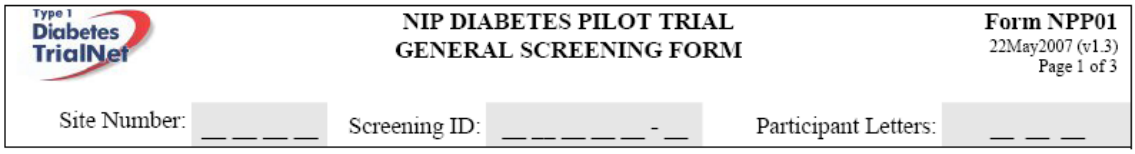
In order to accurately code adverse events and concomitant medications, it is especially important to use correct spelling for diagnoses/symptoms and drug names.

Remove all identifying information (such as subject's name) from the subject data attached to the CRF.

2.1. Completing the Header

All header information must be present on every page and must be identical throughout all the forms.

The following header appears at the top of all pages of every form:



- **Site Number:** Assigned by TrialNet Coordinating Center. Do not leave any blank spaces. Always complete the site number with precedent ceros. If your site number is 4, complete the information as 0004. See Appendix E for site numbers.

- **Screening ID.** The Subject ID Number is an 6-digit number. The Subject ID will be assigned at the screening visit and used for all subjects (Screen Failure and Randomized) throughout the trial. Every site is provided with a list of screening numbers to be used during the study. See Appendix E for screening ID numbers assigned to the sites.

- **Participant letters.** Complete this field using the three letters chosen by the subject during the screening visit. This letter must remain the same for the duration of the study.

If the site needs more Screening numbers, please contact Sara Adams at 301-231-6867.

2.2. Completing the Footer

The following footer appears on the bottom of the last page of all case report forms used in this study:

Initials (first, middle, last) of person completing this form: _ _ _ (F M L)

Date form completed: _ _ / _ _ _ / _ _ _ _ (DAY / MONTH / YEAR)

Initials of person completing the form: The initials of the person completing each form should be placed in the box. If the person doesn't have a middle initial, enter a dash in the middle box (e.g., site coordinator *AB* is recorded as *A-B*). These initials will be recorded and used if the TNCC needs to contact the clinic with any questions about the completion of the form.

Date Form Completed: Date the form was completed by the Site Coordinator or designee.

2.3. Yes/No Fields

Questions requiring a yes or no response will be indicated with a Y for Yes and an N for No. Circle the correct letter to indicate the response to the question.

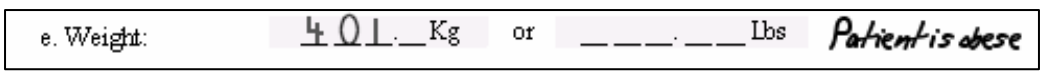
2.4. Checkbox Fields

Fields offering several options using a checkbox format should be carefully reviewed to make sure the appropriate number of responses are selected. Some checkbox fields only allow one response while other checkbox fields allow more than one response. When recording the response, enter a √ or an X into the box.

2.5. The Use of Comments

Additional comments can be attached to **any** gray field on **any** of the data collection forms. These comments are used when the Research Assistant is reviewing the edits. If the comment included on the form sufficiently explains the edit, then the issue will be considered resolved, and the edit will not be forwarded to the clinical center. The comments are also used during the analysis of the data collection forms.

Anyone completing the data collection forms is strongly encouraged to enter comments for any piece of information that would be considered to be helpful in the interpretation of the data. An example of the potential utility of a comment is illustrated below:



Without the comment, this value for the participant's weight would have generated an edit that would have been reviewed by the Research Assistant and then sent on to the clinic for clarification. The presence of the comment lets the Research Assistant know that the person completing the form was aware of the extreme value, and therefore an edit does not need to be sent to the clinic for further verification.

2.6. Missing Value Codes

There are two predefined codes that can be used when completing any of the data collection forms for this or any TrialNet Study. These codes are used to offer an explanation for a missing value to a particular question on the form. If the answer to a particular question is not available when the form is being completed, one of these codes can be entered. This will tell the official database the reason for the missing value. The two codes are as follows:

"*" – The asterisk indicates that the value is permanently missing and will not be available at any future time. The official database will then know not to send any edits regarding this missing value.

"?" - The question mark indicates that the value is currently unavailable (at the time this form is being completed), but is being checked and will be available in the future. The official database then knows to generate an edit regarding this missing value to remind the clinic that it was being checked on.

These two codes can be entered anywhere in the gray shaded response area for a particular question.

The following footer appears on the bottom of every page of every case report form as a reminder of these missing value codes:

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates. Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

3. The Edit System

The edit system is built into the official study database. This system is designed to automatically capture such potential errors in form completion as: missing values, unexpected values, missing value codes, and information on a study form that is either inconsistent or out of range. The edits are generated and then sent to the clinic for resolution.

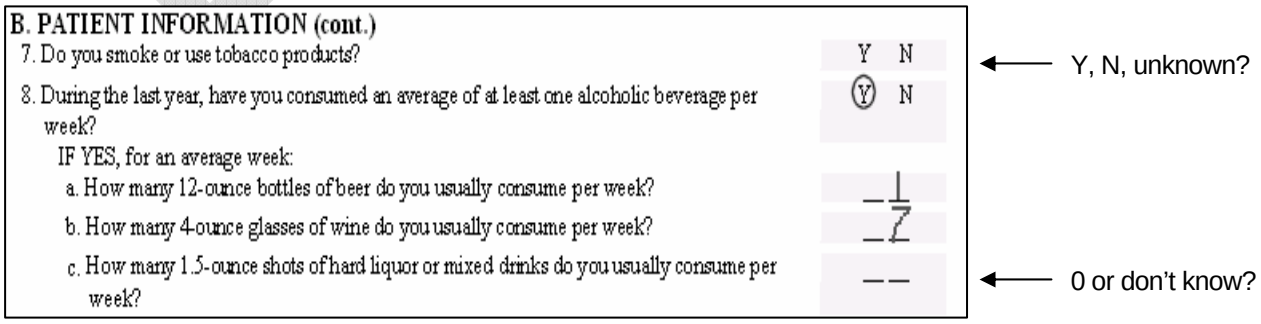
The clinic completes the edit forms and mails them back to the Coordinating Center within two weeks after the site has received the edits. The Coordinating Center reviews the response received and, if deemed adequate, updates the official study database. If the response does not completely resolve the issue that generated the edit, a follow-up edit will be sent to the clinic for further clarification. If an edit is sent to the clinic and no response is received within 4 weeks, a follow-up edit will automatically be generated by the study database, reviewed by the study Research Assistant, and sent to the clinic for resolution. Edits will continue to be sent until a correction is received back from the site and the corrected information is entered into the database.

3.1. Types of Edits

There are many different edits that can be generated, but all of them tend to fall into four broad categories.

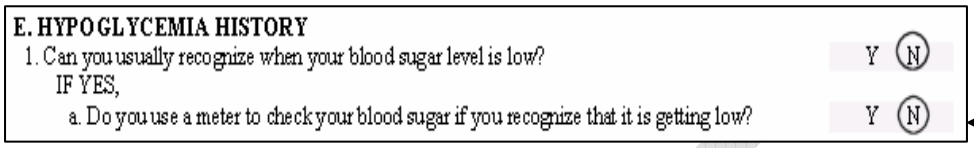
Missing Values

A particular question on a form was not answered. Illustrated by the following example:



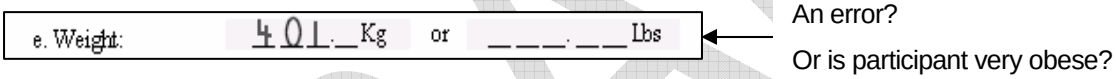
Unexpected Answers

A particular question was unexpectedly answered; say for example that a conditional sub-question was answered despite the condition for answering the question not being met. This is demonstrated in the following example:



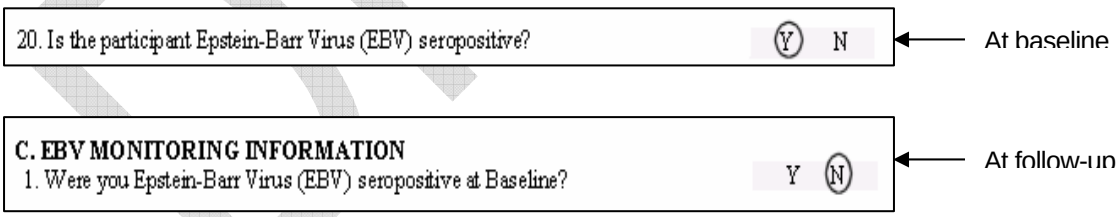
Range Checks

The answer for a particular question is out of a predefined range of "normal". This means the value indicated was either very high or very low. The answer provided may be correct, but the edit is generated to be sure that an error has not occurred due to the peculiarity of the value recorded. This is illustrated in the following example:



Consistency Checks

The answer for a particular question on one form is not consistent with the answer given on a previous form for the same participant. This is illustrated in the following example:



3.2. Common Problems with Form Completion

There are several common problems that are encountered when completing the data collection forms that need to be kept in mind.

Skip Patterns

These are sections that are labeled "IF YES" (or similar language). These sections should **only** be completed when the condition applies, and should be **left blank** otherwise.

Dates

There are two problems that are commonly encountered when dates are entered on the data collection forms. The first is called the "January problem". This problem is encountered during the early part of the New Year, when a common mistake is to write the previous year. This will cause the official database to generate an edit, since the date written on the form is clearly out of the expected range.

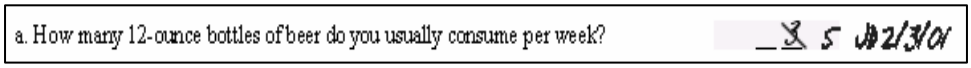
The second problem commonly encountered with dates involves the switching of the month and day elements. To avoid this problem, keep in mind that all dates written on the data collection forms should be in the format: **DAY/MONTH/YEAR** and the month should be in character format NOT numeric.

4. Corrections to Data Forms

When a correction needs to be made to a data collection form, the following guidelines need to be followed:

- Corrections need to be made in **black** ballpoint pen
- The original value needs to be crossed out with a single line so that the original entry remains legible
- The correction should be made on the right of and immediately adjacent to the original entry
- The change should be dated and confirmed with initials

The proper way to make a correction to a data collection form is demonstrated below:



CHAPTER 17 SUMMARY OF NIP PILOT DATA FORMS

The following is a brief summary of each data form for this study. All study forms are to be completed by site study personnel (e.g. Trial/Study Coordinator, etc.) with the exception of NPP20, NPP20E, NPP20M and NPP22, which will be completed by the participant. See Appendix ___ .

There are three different types of Forms for the NIP Pilot study:

- Study Specific Forms: these are the Case Report Forms for the study
- Checklist Forms: these forms are provided as a guide for the site coordinator during each visit. To be kept on site.
- Study Transmittal Forms: for laboratory specimen collection. Information about this forms are found on the laboratory section of the manual.

The forms are provided to the site as Carbon paper forms. Each form has an original (white) and a copy (pink). The original (white) page must be sent to TrialNet via FeDex **within 2 weeks** after the visit. The pink copy should be kept at the site. The forms can be found at the TrialNet Webstie. To determine which forms to use in every visit, review the specific Checklist developed for the visit.

Study Specific Forms

1. **General Screening Form (NPP01)**

   This form is to be completed at either screening visit: (Entry A Pregnant Woman Screening or Entry B Infant Screening) following the completion of the necessary Informed Consent documentation. It is meant to be the first assessment of the participant's eligibility for the study. It also gathers demographic information and the infant's diabetes history.

2. **Pregnant Woman Screening Form (NPP02)**

   The purpose of this form is to assess the pregnant woman's eligibility for randomization into the study. This form collects the pregnancy history including immunization, Omega-3 fatty acid supplementation, and any medications taken during pregnancy.

3. **Pregnant Woman Enrollment Form (NPP03)**

   This form is completed after randomization to collect the participant's medical history and to document the blood samples collected at enrollment.

4. **Infant Screening Form (NPP04)**

   The purpose of this form is to assess the infant's eligibility (newborn to 5 months old) for randomization into the study. This form collects the infant's birth history, medications, physical exam, and demographic information along with the mother's recent pregnancy history and documents blood specimen collections. In the case of multiple births, complete this form for each infant at this screening study visit

5. **Pregnancy History Form (NPP05)**

   This form is to be completed at the infant enrollment visit. On this form the site coordinator will indicate when there is more than one screened infant from one family at the screening study visit.

6. **Infant Enrollment Medical History Form (NPP06)**

   This form is completed at the enrollment study visit, which is the first visit after HLA results are known (1 month after the screening visit) and the infant is determined eligible. This visit may occur when the infant is 1 month to 6 months old. If the infant is 3 or 6 months old at this visit, those visit activities will need to be completed as well.

7. **Infant Family History Form (NPP07)**

   This form is completed at the infant enrollment visit. It does not need to be completed if it was previously completed for a full sibling.

8. **Entry A: Non-Nursing Mother Visit Form (NPP08)**

   This form collects mother-related information when she is not nursing and only if the infant is eligible. This information is collected at the Infant Enrollment Visit.

9. Nursing Mother Visit Form (NPP09)

This form collects nursing mother-related information and is completed at all scheduled visits. No specimens are collected at the Infant Screening Visit.

10. Infant Follow-up Visit Form (NPP10)

This form collects infant related information and is completed at each three month visit except when there is an infant enrollment visit combined with either a 3 month old or a 6 month old visit.

11. Infant 6, 12, 18, 24, and Every 6 Month Old Visit Form (NPP11)

This form collects infant related information and is completed at each six month visit including physical examination and vaccinations.

12. 6, 18, 30 and every 6 month Infant Specimen Collection Form (NPP12)

This form is completed at 6, 18, 30 and every 6 months study visit to record which specimens were collected.

13. 12 Month Old Infant Specimen Collection Form (NPP13)

This form is completed during the 12 months old study visit to record which specimens were collected.

14. 24 Month Old Infant Specimen Collection Form (NPP14)

This form is completed during the 24 months old study visit to record which specimens were collected.

15. Study Substance Dispensation and Return Form (NPP15)

This form is to be completed every time dispensation is performed and any time study substance is returned including any unscheduled visits.

16. Study Substance Compliance Form (NPP16)

This form records compliance of the parent(s) or legal guardian to give the study substance to the infant or of the pregnant or nursing mother to take the study substance. This form is completed at the Entry A Infant Screening, Entry A Infant enrollment, 3, 6, 9 and 12 months visit and every 3 months thereafter while the mother or the participant (infant) is taking study substance or until the participant reaches age 36 months of age.

17. Missed Visit Form (NPP17)

This form is completed when a mother and/or infant misses a scheduled visit.

18. Participant Status Form (NPP18)

This form is completed if a participant (pregnant mother's unborn infant or infant) changes study status (e.g. active, inactive, withdraws, determined to be ineligible, etc).

19. Protocol Deviation Form (NPP19)

This form is completed if there is a protocol deviation. Complete a separate form for mother and infant.

20. Infant Vitamin and Dietary Supplement Form (NPP20)

Complete this form at the infant screening visit, infant enrollment visit, and at the 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, and 48 Months old visits. This form collects the type and frequency of vitamins and dietary supplements the infant has taken in the last 3 months. It is completed by the participant's family. Spanish translation is available.

21. All Mothers Infant Enrollment Vitamin and Dietary Supplement Form (NPP20E)

Complete this from at the Infant Enrollment Visit. This form collects the type and frequency of vitamins and dietary supplements all birth mothers has taken in the last 3 months. It is completed by the participant's family. Spanish translation is available.

22. Pregnant Woman/Nursing Mother Vitamin and Dietary Supplement Form (NPP20M)

Complete this form at the pregnant screening/enrollment visit, infant screening visit, 3, 6, 9, and 12 Month Old Visits. This form collects the type and frequency of vitamins and dietary supplements the pregnant woman or nursing mother has taken in the last 3 months. It is completed by the participant's family. Spanish translation is available.

23. Infant Food Introduction History Form (NPP21)

Complete this form at the Infant Enrollment Visit and at all scheduled visits thereafter. This form record the age when an infant is introduced to the specified foods listed.

24. Mother Food Frequency Questionnaire Form (NPP22)

Complete this form at the pregnant screening/enrollment visit, infant screening and enrollment visit, 3, 6, 9, and 12 Month Old Visits. This form collects the frequency of certain foods eaten by nursing mothers and infants in the last 3 months. It is completed by the participant's family. Spanish translation is available.

25. Adverse Event Form (NPP23)

This form is completed for any new adverse event (either reported or observed) for pregnant woman or infant, whether serious or non-serious, as well as any changes in intensity, frequency, or duration of a previously reported adverse event, even if the adverse event is the same. This form should include the event description, relationship and actions taken, and the event outcome. This form should be sent to the TrialNet Coordinating Center within 24 hours of notification if Grade 3 or above.

26. Med Watch Form

This form is completed to record the details of any Serious Adverse Events (Grade 3 or above) that occur during this study. Complete this form with as much information as is known and fax to the TrialNet Coordinating Center at within 24 hours of clinical notification that en event occurred.

27. Type 1 Diabetes Onset Form (NPP24)

This form is completed when the participant (infant) is diagnosed with Type 1 Diabetes.

28. Entry A: Verification of Infant Eligibility Form (NPP25)

This form is completed during the infant enrollment visit for infants who enter through Entry A.

29. Study Substance Permanent Discontinuation Form (NPP26)

Complete this form for mother/infant who discontinues use of the study formula and/or capsules. The Report date should be the date that information was received from the participant. The participant may report study substance discontinuation at a visit or over the phone.

30. Eligibility and Deviation Review Form

Complete this form for review by the Eligibility Committee if there is a concern regarding an eligibility issue or deviation.

Checklist Forms

Checklist forms are provided as a supplement to the site's source documentation and as a guide for study visits. Checklists don't replace source documents. Checklists are for local site use ONLY, and are not transmitted to the TrialNet Coordinating Center. The following is a brief summary of each checklist for this study. They can be found on the TrialNet Website.

1. Pregnant Woman Screening/Enrollment Visit Checklist (NCL01)

This checklist is to assist the site coordinator in determining which forms and activities are to take place at the Pregnant Woman Screening visit.

2. Infant Delivery Checklist Entry A (NCL02)

This checklist is to assist the site coordinator in determining which forms and activities are to take place at the Infant Delivery.

3. **Infant Screening Visit Checklist 2 to 28 Days from Delivery Entry A (NCL03)**

   This checklist is to assist the site coordinator in determining which forms and activities are to take place at the Infant Screening Visit for those infants who entered the study prenatal.

4. **Infant Screening Visit Entry B Checklist (NCL04)**

   This checklist is to assist the site coordinator in determining which forms and activities are to take place at the Infant Screening Visit for those infants who entered after birth.

5. **Infant Enrollment Visit Checklist Entry A (NCL05)**

   This checklist is to assist the site coordinator in determining which forms and activities are to take place at the Infant Enrollment Visit.

6. **Infant Enrollment Visit Checklist Entry B (NCL06)**

   This checklist is to assist the site coordinator in determining which forms and activities are to take place at the 3 Month Interval visits.

7. **Non-Qualified Debriefing Visit Checklist (NCL07)**

   This checklist is to assist the site coordinator in determining which forms and activities are to take place when the participant is not qualified to continue in the study.

8. **Mother Follow-Up Visit Checklist (NCL08)**

   This checklist is to assist the site coordinator in determining which forms and activities are to take place at the 3, 9, 15, and 21 month old visits.

9. **Infant and Mother Follow-Up Visit Checklist (NCL09)**

   This checklist is to assist the site coordinator in determining which forms and activities are to take place at the 6, 12, 18, 24 and every 6 month old visits.

10. **Infant Enrollment Visit Checklist (NCL10)**

This checklist is to assist the site coordinator in determining which forms and activities are to take place when the Infant Enrollment Visit is combined with the Entry A infant screening visit.

CHAPTER 18 LABORATORY PROCEDURES

1. Overview

Two types of laboratories will be used for the NIP Pilot Trial: Core laboratories and Local laboratories, depending on the test.

Make sure to review the visit specific Checklists to determine which tests will be done at each visit and what STFs need to be used. Samples collected for storage will be sent to the CORE ICA laboratory.

2. Local Laboratory

Only HbA1c and glucose will be done at local laboratories. Trial Coordinator must identify the local laboratories to be used for these tests and send all the required information to the TrialNet Coordinating Center.

HbA1c: Pregnant women with diabetes will need an HbA1c test before enrolling through Entry A. Pregnant women with an HbA1c greater than 9% will not be permitted to screen through Entry A. They may choose to screen the infant through Entry B after the delivery.

3. Core Laboratories: Shipping Locations and Addresses for Blood Specimens

All other samples for the NIP Diabetes Pilot will be analyzed by TrialNet Laboratories. Refer to the NIP Diabetes Specimen Collection Instructions for detailed collection, processing and shipping information.

3.1. CHORI HLA Lab

Address:	Attn: Steve Mack ROCHE Molecular Systems Human Genetics Department 1145 Atlantic Ave. Alameda, CA 94501
Phone:	(510) 814-2949
Samples:	• Infant HLA

3.2. TrialNet Core ICA Laboratory

Address:	TrialNet Core Screening Laboratory (UFDRL) University of Florida 4800 SW 35th Drive Gainesville, FL 32608
Phone:	(352) 265-9900
Samples:	• Infant and Mother Autoantibodies • Infant and Mother Fatty Acids (RBC) and Inflammatory Mediators • Nursing Mother Fatty Acids (Breast Milk) • Infant PBMCs and Plasma

3.3. TrialNet Core Biochemistry Laboratory (NWLRL)

Address:	Specimen Processing Northwest Lipid Research Laboratories University of Washington 401 Queen Anne Ave. North Seattle, WA 98109
Phone:	(206) 685-3331 (206) 685-3327
Samples:	• Infant and Mother Vitamin D and CRP

3.4. TrialNet Core Viral Laboratory

Address:	University of Colorado Health Sciences Center 4200 East 9th Ave Room MS1632 Denver, CO 80262
Phone:	(303) 315-1760
Samples:	• Tetanus LPA

3.5. TrialNet Core Viral Laboratory

Address:	University of Colorado Health Sciences Center Viral Lab 4200 East 9th Ave Room CC029 Denver, CO 80262
Phone:	(303) 372-0522
Samples:	• Tetanus Viral Serology

3.6. NIDDK Repository (Stored Samples)

Address:	Director: Heather Higgins **NIDDK REPOSITORY** Fisher BioServices 20301 Century Blvd. Building 6, Suite 400 Germantown, MD 20874
Phone:	**(240) 686- 4702**
Samples:	• Residual Samples • Plasma • PBMC

4. Total Blood Volumes Drawn

The minimum amount of blood drawn at any visit is 1.0 ml, which will be drawn for the HLA typing and Islet Autoantibodies by heel stick at the Infant Screening Visit. The maximum amount of blood drawn at any visit is 24 ml which will be collected as cord blood at the Infant Delivery.

4.1. Specimen Transmittal Forms

Specimen transmittal forms (STFs) must accompany all samples sent to the laboratory for analysis. These forms capture participant information for the sample, as well as the date and visit at which the sample was collected. The STFs all have space for the appropriate barcode labels to be attached, as well as to record the contact information of the person who shipped the samples. The following page provides a sample specimen transmittal form and highlights its important features. The specimen transmittal forms are printed on 3-sheet NCR paper. Always remember that:

- The **white copy** should always be sent to the TrialNet Coordinating Center.
- The **yellow copy** should always be sent to the laboratory with the samples for analysis.
- The **pink copy** should be kept at the clinic as part of the source document.

Do not forget to mail the White copy of the STF to TrialNet. Without this copy, TrialNet cannot report the laboratory data on the website

The following is a list of specimen transmittal form (STF) for this study. A copy of each STF is found in the TrialNet Web site – NIP study.

- Infant Biochemical Autoantibodies (NP99IAA)
- Infant Vitamin D & C-Reactive Protein (NP991DC)
- Infant Fatty Acids (RBC) & Inflammatory Mediators (NP991FM)
- Infant Human Leukocyte Antigen (HLA)/DNA (NP99IHL)
- Infant PBMCs and Plasma Collection (NP991PP)
- Infant Tetanus Autoantibody Serology (NP99ITA)
- Infant Tetanus LPA Cellular Response (NP99ITL)
- Mother Biochemical Autoantibodies (NP99MAA)
- Mother Vitamin D & C-Reactive Protein (CRP) (NP99MDC)
- Mother Fatty Acids (Breast Milk) (NP99MFB)
- Mother Fatty Acids (RBC) & Inflammatory Mediators (NP99MFM)

NOTE:
In the case of twins, complete mother case report forms only once, but complete separate infant case report forms and blood draws for each child.

4.3. Sample Specimen Transmittal Form (NP99IAA)

The following is an example of the NIP STFs.

The **header** is used to record information on the participant the sample is collected from.

Section A also captures information on when the specimen was collected and for which visit.

Section A always contains instructions for collecting the blood samples.

Section B always contains shipping instructions for the samples.

Section C is for lab use only.

Type 1 Diabetes TrialNet

NIP DIABETES PILOT TRIAL
INFANT BIOCHEMICAL AUTOANTIBODIES
SPECIMEN TRANSMITTAL FORM

Form NP99IAA
20Oct2006 (v1.0)
Page 1 of 1

Site Number: _ _ _ _ _ Screening ID: _ _ _ _ _ _ _ - _ _ Participant Letters: _ _ _ _

Complete this STF for INFANT specimen collections. Follow the specimen processing, handling, and shipping instructions in the NIP Diabetes Pilot Specimen Collection Instructions.

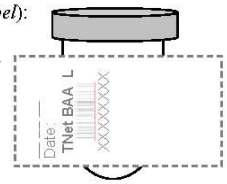
A. SPECIMEN INFORMATION

1. Date specimen collected (*e.g. 05/Sep/2006*): _ _ / _ _ _ _ _ / _ _ _ _ _ (DAY / MONTH / YEAR)
2. Time specimen collected (*e.g. 13:36*): _ _ : _ _ (Hour : Min)
3. For which study visit is this form being completed (*check only one*):

☐92	Delivery	☐12	12 Months Old	☐30	30 Months Old	☐48	48 Months Old
☐1	Infant Screening	☐18	18 Months Old	☐36	36 Months Old	☐99	Other, a. specify date:
☐6	6 Months Old	☐24	24 Months Old	☐42	42 Months Old		_ _ / _ _ _ _ _ / _ _ _ _ _ (DAY / MONTH / YEAR)

4. Specimen source (*check only one*): ☐1 Cord blood ☐2 Capillary blood (by heel stick) ☐3 Venous blood
5. Was specimen collected to confirm 2 or more autoantibodies? Y N
6. Place **BAA** Barcode Label Here (*Remember to write "B" on the specimen's label*):

A barcode label from the **same sheet** as the labels put on the specimen tubes must be attached here.



B. SHIPPING INFORMATION

- Follow the NIP Diabetes Pilot Specimen Collection Instructions to BATCH SHIP FROZEN specimens.
- Prepare and print a pre-paid airbill to FedEx all specimens **Priority Overnight** to the TrialNet Core Screening Laboratory (UFDRL) (see NIP Diabetes Pilot Specimen Collection Instructions for address).

1. Shipped By Name: 2. Phone #:
3. Date Shipped: _ _ / _ _ _ _ / _ _ _ _ _ (DAY / MONTH / YEAR) 4. Comments:

C. For TrialNet Core Lab Use Only

Sample Received? Y N Date Received: _ _ / _ _ _ _ / _ _ _ _ _ (DAY / MONTH / YEAR) **Place Lab Barcode Label Here**

Comments:

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates. Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

White Copy – Send to TrialNet Coordinating Center **Yellow Copy** – Place in outside sleeve of the biohazard Ziploc bag
Pink Copy – Retain at site

5. Barcode Label Sheets

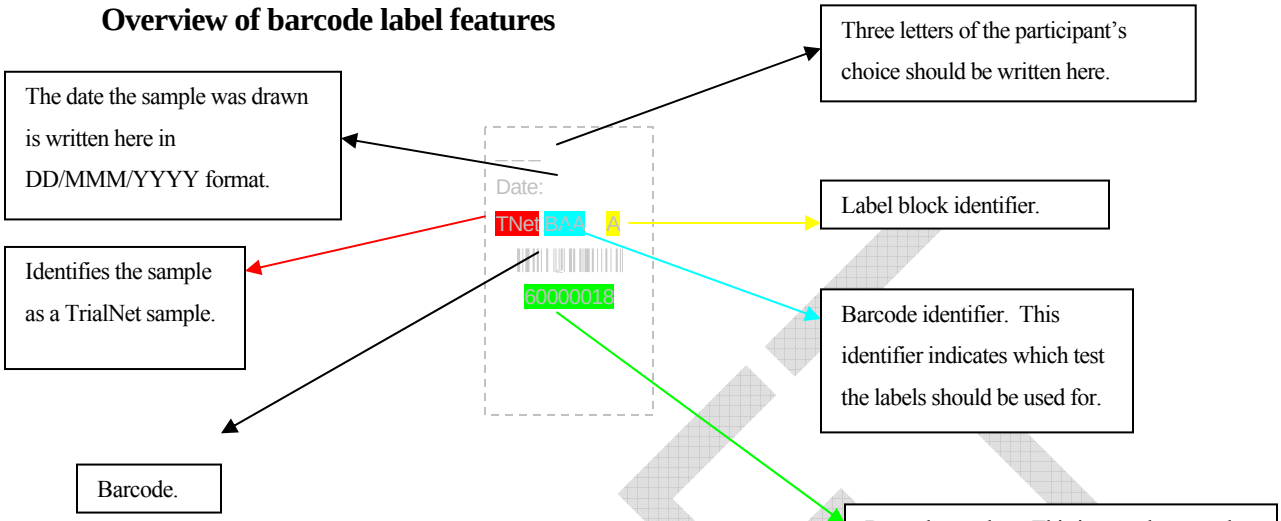
Prior to the initiation of any study procedures all participating sites will receive batches of fan-folded barcode label sheets for every test that is run as part of the NIP Diabetes Pilot Trial. Each batch of label sheets will correspond to a single type of test, and each block of labels on the sheet will be used for only one test. For example, each site will receive a batch of fan-folded barcode label sheets for the HLA test. Every time an HLA test is run on a study participant, a new block of barcode labels will be used.

5.1. Format of Sheets and Labels

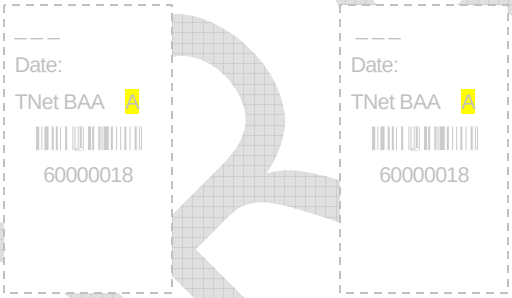
The barcode labels will be provided in fan-folded sheets. Each block of barcode labels is to be used for a single test. A letter in the upper right corner of the label distinguishes each block of labels. All labels in a single block will have the same letter in the upper right corner. One label from the block should be put on each of the three copies of the specimen transmittal form (total of three labels used). The remaining labels in the block should be placed on the specimen tube(s) or vial(s). There may be a couple of extra barcode labels included in the block, in the event that any labels are damaged or lost.

It is absolutely crucial that every copy of the specimen transmittal form contains a barcode label from the SAME BLOCK as the labels placed on the specimen tubes or vials! If this does not occur, there will be no way to link the laboratory samples to a study participant!

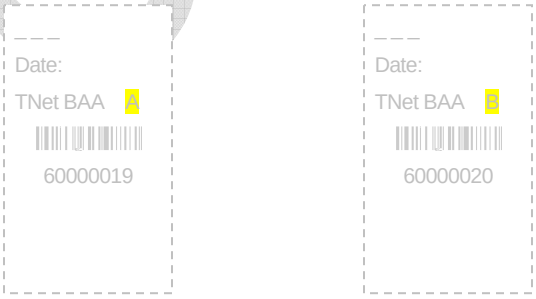
Overview of barcode label features



Examples of barcode labels from the SAME BLOCK:



Examples of barcode labels from DIFFERENT BLOCKS:



5.2. Barcode Label Identification

The following table summarizes the barcode labels that should be used for each test that is part of this study:

Test Name	Barcode Identifier
HLA	HLA
Infant and Mother Autoantibodies	BAA
Infant and Mother Inflammatory Mediators	IFM/FA
Infant and Mother Vitamin D and CRP	D/CRP
Nursing Mother Fatty Acids (Breast Milk)	FA(BM)
Infant PBMCs and Plasma	PBMC
Infant Tetanus Autoantibody Serology	TETAB
Infant Tetanus LPA Cellular Response	TETLPA

The barcode identifier can be found above the barcode. This identifier makes it easier to differentiate between barcode labels for different tests.

5.3. Ordering Barcode Label Sheets

If more fan-folded barcode label sheets are needed, they should be requested from the TrialNet Coordinating Center through the Clinical Online Ordering System.
https://www.fisherbio.com/client/bsdweb/trialnet/Login.asp

CHAPTER 19 SUPPLIES

Case Report Forms (CRFs), Specimen Transmittal Forms (STFs), Participant Binders (pre-filled with all visit checklists and dividers, and CRFs and STFs through Month 3), barcode labels, and other study supplies are provided to all study sites by the TrialNet Coordinating Center (TNCC).

Site Coordinators will use the online Supply Ordering System to order any of the supplies needed. There is a link to the Supply Order System "SOS" on the TrialNet Study website https://www.diabetestrialnet.org under Supplies Ordering.

There is a separate link for ordering Public Relations materials.

Technical support for problems on using the web order system is available. A User Manual may also be downloaded from the above website address.

Sites will receive an initial quantity of screening supplies just prior to receiving approval to begin screening. Generally, sites should maintain a 3-month inventory or longer, sufficient for study needs. This is to avoid frequent reordering of supplies.

1. Ordering Clinical Supplies

A central supplies distributor will be responsible for processing orders of clinical supplies for blood collections and shipments. TNCC, through its subcontractor ThermoFisher Bioservices, implemented a web based online order system for all supplies. "Authorized users", those individuals responsible for study supplies at the site, are provided with a login and password for the web order system. Webcast training on use of the web order system is provided by the TNCC.

1.1. Authorized Users

Only staff at your site that has been authorized to submit orders will be issued a user account (login and password). All Site Coordinators are authorized users when the site receives site certification from TrialNet. The Site Coordinator wishing to request additional user accounts for staff at their site should email a request to TNOrders@bsc.gwu.edu at the TNCC with "Request SOS User" in the subject line. The request should identify the position or role (e.g., research staff) and provide the full name and email address of the new user.

1.2. TrialNet Supply Order System "SOS" (Web Application)

Clinical supplies are available through Fisher Bioservices which is part of ThermoFisher Scientific. There is a link to the Supply Order System "SOS" on the TrialNet Study website https://www.diabetestrialnet.org under Supplies Ordering. There is a separate link for ordering Public Relations materials.

Technical support for problems on using the web order system is available. A User Manual may also be downloaded from the above website address.

CHAPTER 20 REIMBURSEMENT

This chapter describes reimbursement for protocol-related activities by the TrialNet Coordinating Center. Reimbursement is according to the NIDDK approved reimbursement schedule for the NIP Diabetes Pilot Trial. Reimbursement is provided for:

- Local laboratory services
- Local medical services
- Local pharmacy services
- Other services
- Study costs

Rates vary for Clinical Centers and Affiliate Sites with and without a GCRC. Refer to the TrialNet Fact Sheet of Reimbursement located on the TrialNet website for more information.

1. Reimbursement Schedule

The TrialNet Clinics will be paid for their screening, enrollment, and follow-up of study participants. Each site will be responsible for the cost of a courier service, if one is used. NIDDK approved reimbursement schedules are posted on the TrialNet website. Payments issued to the Clinical Centers/Major Affiliates and Affiliate Sites are based on complete/accurate forms submitted to the GWU TNCC. All payments will be made in United States dollars. Payments should be generated and mailed within 30 days of the close of the payment period. An Invoice Report and a detailed listing of services being reimbursed will be provided to the sites along with the payment.

Reimbursements for all components of a visit are made to the site that completed the visit. All applicable Case Report Forms have a place for recording the Site Number for reimbursement. This number is a unique number to identify the institution where the visit took place.

CHAPTER 21 QUALITY CONTROL SYSTEM OF SAMPLES

In order to determine the near-term repeatability of assays, reflecting all sources of potential errors, from the point of sample collection to statistical analysis, split duplicate analysis will be performed on specimens collected from study participants. Split duplicates will only be drawn on participating mothers. Infants will not have any extra blood draws. This program has yet to be implemented for this study. Information on this program will be provided as it becomes available.

Appendix A. Volunteer Understanding Survey Key – Enrollment During Pregnancy and Infant Enrollment

Type 1 Diabetes TrialNet

NIP Diabetes Pilot Study
VOLUNTEER UNDERSTANDING SURVEY
Enrollment During Pregnancy

Form NPPPVQ
June 14, 2006
Version 1.0

Site ID: __ __ __ __ Screening ID: __ __ __ __ __ - __ Participant Letters: __ __ __

Volunteer Understanding Survey is based on the information that has been presented to you regarding this clinical research study. All of the questions are based on this information. The purpose of this survey is to be sure you know the details of this clinical research study before you agree to be part of it. After you have finished the survey, the research study team will go over the answers with you. The research study team will be sure to discuss any answers that were incorrect, because it is important to us that you understand the study.

Date the survey was completed: __ __ / __ __ / __ __ __ __
DAY MONTH YEAR

Put an "X" or a check in the box next to the best answer(s) to each question.
You may take as much time as you want to answer these questions.

1. My baby will not need further testing to be in the study if I join during my pregnancy.
   - ☐ 1 True
   - ☒ 2 False
   - ☐ 3 I do not know

2. An important reason for doing this study is to see:
   - ☒ 1 If a larger and longer study is feasible.
   - ☐ 2 How many babies develop type 1 diabetes
   - ☐ 3 How many babies develop autoantibodies
   - ☐ 4 I do not know

3. If I decide to be in this research study, my baby and I will be expected to participate in the study for a minimum of:
   - ☒ 1 1 year and possibly longer
   - ☐ 2 Less than 1 year
   - ☐ 3 6 months
   - ☐ 4 I do not know

4. If I decide to be in this research study, I will be expected to bring my baby to the study site:
   - ☐ 1 Every three months
   - ☒ 2 Every six months
   - ☐ 3 Once a year
   - ☐ 4 I do not know

5. If I agree to be in this research study, I will be expected to *(check all that apply)*:
   - ☒ 1 Use the study treatment capsules and formula provided by the study
   - ☒ 2 Stay in the treatment group I am assigned to until the research study ends
   - ☒ 3 Keep all appointments at the clinic
   - ☐ 4 I do not know

6. My assignment to a treatment group will be random (like the flip of a coin). This means:
   - ☒ 1 I will have 1 out of 2 chances of being in the treatment group
   - ☐ 2 I can choose which treatment group I want to be in
   - ☐ 3 My doctor will choose the treatment group that is best for me
   - ☐ 4 I do not know

Type 1 Diabetes TrialNet	NIP Diabetes Pilot Study VOLUNTEER UNDERSTANDING SURVEY Enrollment During Pregnancy	Form NPPPVQ June 14, 2006 Version 1.0 Page 2 of 3
Site ID: __ __ __ __	Screening ID: __ __ __ __ __ __ - __	Participant Letters: __ __ __

7. Participation in this research study is voluntary. Which of the following is also true? *(check all that apply)*
   - ☒ 1 I can choose to not be in this research study or to stop being in this research study at any time
   - ☒ 2 I should let the investigator know if I choose to stop being in the study
   - ☒ 3 If I choose not to continue taking the study treatment I will be asked to still come for study visits.
   - ☐ 4 I do not know

8. The risks of being in this research study may include *(check all that apply)*:
   - ☒ 1 Bruising from blood tests.
   - ☒ 2 Burping or reflux
   - ☒ 3 Skin rashes
   - ☐ 4 I do not know

9. HLA genes (genetic testing) can tell us:
   - ☐ 1 If someone will definitely get diabetes
   - ☐ 2 If someone will definitely not get diabetes
   - ☒ 3 If someone is at higher or lower risk for getting diabetes
   - ☐ 4 I do not know

10. If I decide to be in this research study *(check all that apply):*
    - ☒ 1 There will be blood tests for me and my baby as required by the study at no cost to me
    - ☒ 2 I will receive capsules and/or infant formula as provided by the study at no cost to me
    - ☒ 3 I will be compensated for time and travel costs
    - ☐ 4 I do not know

11. If I decide to be in this research study during pregnancy, I will need to take the study capsules as follows:
    - ☐ 1 One capsule daily
    - ☐ 2 Two capsules daily
    - ☐ 3 Three capsules daily
    - ☒ 4 Four capsules daily
    - ☐ 5 I do not know

12. When my enrolled baby is one year of age, I will give the study capsules as follows:
    - ☐ 1 Add one capsule daily to my baby's diet (by mixing them into food or beverages)
    - ☒ 2 Add two capsules daily to my baby's diet (by mixing them into food or beverages)
    - ☐ 2 Add three capsules daily to my baby's diet (by mixing them into food or beverages)
    - ☐ 2 Add four capsules daily to my baby's diet (by mixing them into food or beverages)
    - ☐ 3 I do not know

13. After my baby is born, I will continue taking the study treatment capsules while waiting to find out if my baby is eligible to be in the study:
    - ☒ 1 True
    - ☐ 2 False
    - ☐ 5 I do not know

Type 1 Diabetes TrialNet	NIP Diabetes Pilot Study VOLUNTEER UNDERSTANDING SURVEY Enrollment During Pregnancy	Form NPPPVQ June 14, 2006 Version 1.0 Page 3 of 3
Site ID: __ __ __ __	Screening ID: __ __ __ __ __ __ - __	Participant Letters: __ __ __

14. If I am nursing my baby, I will need to bring a breast milk sample to the study clinic as follows:
- ☐ 1 A sample must be brought to the clinic once every six months
- ☒ 2 A sample must be brought to the clinic every three months
- ☐ 3 Bringing a sample is optional if nursing
- ☐ 4 I do not know

15. While I am in the study, I can use a combination of the study formula and other formulas of my choice for feeding my baby:
- ☐ 1 True
- ☒ 2 False
- ☐ 3 I do not know

16. My baby will no longer be able to be in the study if he/she develops two or more autoantibodies (confirmed on two separate visits):
- ☒ 1 True
- ☐ 2 False
- ☐ 3 I do not know

Type 1 Diabetes TrialNet

NIP Diabetes Pilot Study
VOLUNTEER UNDERSTANDING SURVEY
Infant Enrollment

Form NPP
06 N
Ver
Pag

Site ID: __ __ __ __

Screening ID: __ __ __ __ __ - __

Participant Letters: __ __

Volunteer Understanding Survey is based on the information that has been presented to you regarding this clinical research study. All of the questions are based on this information. The purpose of this survey is to b sure you know the details of this clinical research study before you agree to be part of it. After you have finished the survey, the research study team will go over the answers with you. The research study team will be sure to discuss any answers that were incorrect, because it is important to us that you understand the study

Date the survey was completed: __ __ / __ __ __ / __ __ __ __
DAY MONTH YEAR

Put an "X" or a check in the box next to the best answer(s) to each question.
You may take as much time as you want to answer these questions.

1. Signing the consent form means my baby will have further testing and will definitely be in the study:
   - ☐ 1 True
   - ☒ 2 False
   - ☐ 3 I do not know

2. An important reason for doing this study is to see:
   - ☒ 1 If a larger and longer study is feasible.
   - ☐ 2 How many babies develop type 1 diabetes
   - ☐ 3 How many babies develop autoantibodies
   - ☐ 4 I do not know

3. If I decide to be in this research study, my baby and I will be expected to come to the study site for a minimum of:
   - ☒ 1 1 year and possibly longer
   - ☐ 2 Less than 1 year
   - ☐ 3 6 months
   - ☐ 4 I do not know

4. If I decide to be in this research study, I will be expected to bring my baby to the study site:
   - ☐ 1 Every three months
   - ☒ 2 Every six months
   - ☐ 3 Once a year
   - ☐ 4 I do not know

5. If I agree to be in this research study, I will be expected to *(check all that apply)*:
   - ☒ 1 Use the study treatment capsules and formula provided by the study
   - ☒ 2 Stay in the treatment group I am assigned to until the research study ends
   - ☒ 3 Keep all appointments at the clinic
   - ☐ 4 I do not know

6. My assignment to a treatment group will be random (like the flip of a coin). This means:
   - ☒ 1 I will have 1 out of 2 chances of being in the treatment group
   - ☐ 2 I can choose which treatment group I want to be in
   - ☐ 3 The doctor decides which treatment group I will be in
   - ☐ 4 I do not know

Type 1 Diabetes TrialNet	NIP Diabetes Pilot Study VOLUNTEER UNDERSTANDING SURVEY Infant Enrollment	Form NPPBVQ 06 Nov 2006 Version 1.1 Page 2 of 2
Site ID: __ __ __ __	Screening ID: __ __ __ __ __ __ - __	Participant Letters: __ __ __

7. Participation in this research study is voluntary. Which of the following is also true? *(check all that apply)*
- ☒ 1 I can choose to not be in this research study or to stop being in this research study at any time
- ☒ 2 I should let the investigator know if I choose to stop being in this study
- ☒ 3 If I choose not to continue taking the study treatment, I will be asked to still come for study visits
- ☐ 4 I do not know

8. The risks of being in this research study may include *(check all that apply)*:
- ☒ 1 Bruising from blood tests
- ☒ 2 Burping or reflux
- ☒ 3 Skin rashes
- ☐ 4 I do not know

9. HLA genes (genetic testing) can tell us:
- ☐ 1 If someone will definitely get diabetes
- ☐ 2 If someone will definitely not get diabetes
- ☒ 3 If someone is at higher or lower risk for getting diabetes
- ☐ 4 I do not know

10. If I decide to be in this research study *(check all that apply)*:
- ☒ 1 There will be blood tests for me and my baby as required by the study at no cost to me
- ☒ 2 I will receive capsules and/or infant formula as provided by the study at no cost to me
- ☒ 3 I will be compensated for time and travel costs
- ☐ 4 I do not know

11. When my enrolled baby is one year of age, I will give the study capsules as follows:
- ☐ 1 Add one capsule daily to my baby's diet (by mixing them into food or beverages)
- ☒ 2 Add two capsules daily to my baby's diet (by mixing them into food or beverages)
- ☐ 3 Add three capsules daily to my baby's diet (by mixing them into food or beverages)
- ☐ 4 Add four capsules daily to my baby's diet (by mixing them into food or beverages)
- ☐ 5 I do not know

12. While I am in the study, I can use a combination of the study formula and other formulas of my choice for feeding my baby:
- ☐ 1 True
- ☒ 2 False
- ☐ 3 I do not know

13. If I am nursing my baby, I will need to bring a breast milk sample to the study clinic as follows:
- ☐ 1 A sample must be brought to the clinic once every six months
- ☒ 2 A sample must be brought to the clinic every three months
- ☐ 3 Bringing a sample is optional if I am nursing
- ☐ 4 I do not know

14. My baby will no longer be able to be in the study if he/she has two or more autoantibodies (confirmed on two separate visits):
- ☒ 1 True
- ☐ 2 False
- ☐ 3 I do not know

Appendix B. Instructions for Requesting the Destruction of Samples

Withdraw of Consent to Store Laboratory Samples:

Participants are NOT required to provide consent for stored samples in order to participate in the study. Participants also have the right to withdraw their consent to store samples at any time and to have their stored samples destroyed. The participant must indicate their choice on the Informed Consent Forms and initial in the appropriate area. There are three options each for the mother and their infant:

If the first choice is selected, all samples (including specimen residuals) may be stored:

☐ Yes, I give permission to have my samples stored including the genetic samples.

If the second choice is selected:

☐ Yes, I give permission to have my samples stored, but NOT the genetic samples.

The only stored samples that fall under the genetic samples category are the following **specimen residuals:**

HLA Typing

Fatty Acids (RBC)

Inflammatory Mediators (RBC)

Tetanus LPA Cellular Response (Green top)

PBMC (obtained at the 24 months old visit)

NOTE: Plasma, serum, and breast milk do not classify as genetic samples.

Collect all required samples, the laboratory will destroy appropriate specimens upon receipt of the Request for Sample Destruction Form.

If the third choice is selected, NO samples (including specimen residuals) may be stored:

☐ No, I do not give permission to have any of my samples stored.

To Request the Destruction of Samples:

Complete the "Request for Sample Destruction" form, have the site Principal Investigator sign, and submit to the TNCC Laboratory Coordinator, Donna Phoebus (Fax: (301) 881- 0179 or "Donna Phoebus" DPhoebus@biostat.bsc.gwu.edu).

The Laboratory Coordinator will review the request, initiate and coordinate the destruction of samples with Core Laboratories/Repository, as appropriate. This will be done via a "Laboratory Notification of Sample Destruction" request form. This document serves as a request for, and confirmation of, specimen destruction.

Upon completion of specimen destruction, the laboratory/Repository will transmit or Fax the signed "Laboratory Notification of Sample Destruction" to the Laboratory Coordinator at the TNCC and keep a copy for their records.

The events will be logged into the "Destroyed Sample Log" maintained by the Laboratory Coordinating Group. The signed "Laboratory Notification of Sample Destruction" form will be kept on file for documentation.

The Laboratory Coordinator will send a written notification to the site Principal Investigator, and copied to the Site Coordinator, by Federal Express confirming that the requested sample(s) have been destroyed per the subject's request.

Sample data/results obtained prior to the date of the subject request will be maintained in the database for the purpose of analysis, but all sample results generated after the request date will not be recorded into the TNCC database or used for analysis purposes.

Request for Sample Destruction

To request the destruction of a patient's stored specimens, fill out the information below and send a copy of this form to the TNCC Lab Coordinator, Donna Phoebus dphoebus@biostat.bsc.gwu.edu or Fax (301-881-0179). The Laboratory Coordinator will review the request, initiate and coordinate the destruction of samples with the Core Laboratories/ Repository, as appropriate.

Upon written notification from the lab(s)/Repository that all specimens have been destroyed, the Laboratory Coordinator will mail a Letter of Confirmation to the site Principal Investigator.

Date of Request: _____

Site Submitting Request (Name): _____ Number _____

Requested by (Name): _____

Study Name: _____

Circumstances/Reason for Sample Destruction:

Signature of Site Principal Investigator: _____ Date: _____

PID	*Lab/ Repository	Assay	Sample Number	Date of Collection

*PID: NIP Specimens must be identified by PID and "Mother" or "Infant"

*Labs/ Repository can be abbreviated as:

"ICA" = ICA lab in Gainesville, FL (ICA)

"**BAA" =** Autoantibody lab in Denver, CO (GAD512, mIAA, ICA512)

"HLA" = HLA lab in Denver, CO (HLA, DNA),

"CHORI" = NIP Study HLA lab in Oakland, CA (HLA)

"Beta" = Beta Cell Function Lab in Seattle, WA (C-peptide, Insulin, HbA1c, Glucose)

"CBL" = Core Biochemical Lab in Seattle, WA (Chemistry panel, Cholesterol, HIV/Hep.B,C, MPA, Glucose, C- Reactive Protein (CRP), Vitamin D)

"Viral" = Virology Laboratory in Denver, CO (HSV, EBV, CMV, Varicella, Rubella, Flu Ab, Tetanus, Hepatitis A, Tetanus/LPA)

"IFM" = Inflammatory Mediator Laboratory in Gainesville, FL (Fatty Acids, Inflammatory Mediators)

"NIDDK" = Repository: National Institute of Digestive, Diabetes, and Kidney (Long term sample storage)

Appendix C. Site Initiation Activities Check

August 17, 2006

Site Initiation Activities for NIP Diabetes Pilot Trial

_____
Site Name

- The following is an internal checklist for use by clinical sites that covers the basic steps for initiating the NIP Diabetes Pilot Trial.
- Check the appropriate box, date and initial to note completion of each item.
- Sections with an * indicate that TNCC must have documentation to verify that this requirement has been satisfied. Fax these items to TNCC Attn: Sue Reilley at (301) 881-0179.
- Once the entire form is complete, print and sign your name at the bottom and fax to Sue Reilley at the number provided above. More than one person may sign if multiple individuals were involved in site initiation activities.
- Keep this document in your Regulatory Binder or Research Files, along with copies of any documents that are sent to TNCC. Each site should also file their protocol activation letter once it is received.

Item	Completed	Date / Initials
Getting Started		
Verify that all NIP Diabetes staff contact information has been correctly updated on the TrialNet website.	☐	
*Complete DU7s for all staff members.	☐	
*FORMULA: Complete the Eminent Services Corporation Clinical Site Contact Information Form to indicate where study formula will be shipped.	☐	
*CAPSULES: Complete the Eminent Services Corporation Clinical Site Contact Information Form to indicate where study capsules will be shipped.	☐	
Availability of -20° C freezer for storage of frozen samples.	☐	
Local courier service (for delivery of formula to participant's home) has been set up.	☐	
A plan for cord blood logistics has been finalized.	☐	
HbA1c		
*Provide name, address and normal value ranges to TNCC for local laboratory that will be performing HbA1c.	☐	
*If above is N/A, provide name, model, and normal value ranges to TNCC for equipment being used to measure HbA1c.	☐	

August 17, 2006

Item	Completed	Date / Initials
Training and Certification		
All staff members have reviewed the current protocol, study procedures, and other study documents.	☐	
*All staff members have completed protocol certification.	☐	
All staff members have reviewed the Adverse Event Monitoring Plan, CTCAE v3, CTCAE Dictionary and Index, and Intensity Grading Criteria for Vasovagal Events under the Adverse Event Reporting & Monitoring section of the TrialNet homepage.	☐	
All staff members have read Section 6 of the protocol, Adverse Event Reporting and Safety Monitoring.	☐	
*Provide TNCC with pass-phrase for web randomization system.	☐	
The Site Coordinator has completed the mock randomization.	☐	
IRB Approval		
*Provide IRB approval letter to TNCC. Ensure the appropriate version and date of protocol is reflected.	☐	
*Provide stamped IRB approved ICFs to TNCC. NOTE: TNCC **must** review and approve consents before a site can start the study.	☐	
Preparing for Implementation		
Initial shipment of laboratory supplies has been received. *NOTE: Use web online system for all re-orders.*	☐	
Initial shipment of participant binders (with study forms), barcode labels, and other materials has been received. *NOTE: Use order form available on website for all re-orders.*	☐	
Initial shipment of study formula has been received, inventoried, and properly stored.	☐	
Initial shipment of study capsules has been received, inventoried, and properly stored.	☐	
Review shipping procedures for TrialNet laboratory samples.	☐	
*Complete University of Florida Confidentiality Agreement and send to TNCC.	☐	
Implementation		
Implementation can begin once the protocol activation letter **is received** by the site from the TNCC.	☐	

_____ _____

Printed Name *Signature*

_____ _____

Printed Name *Signature*

Appendix D. Eligibility and Deviation Review Form

Type 1 Diabetes TrialNet

ELIGIBILITY AND DEVIATION REVIEW FORM

Form ELIG
16MAY2007
Page 1 of 1

Study: **NIP Diabetes Pilot** Screening ID: __ __ __ __ __ - __ Issue Number: __ __ __

A. GENERAL INFORMATION

1. Date of review request: __/__/____ (DAY/MONTH/YEAR)
2. Date response needed by: __/__/____ (DAY/MONTH/YEAR)

B. GENERAL SUBJECT INFORMATION

1. NIP Diabetes Pilot Entry Pathway: ☐1 Entry A Pregnant Woman ☐2 Entry B Infant
2. Eligibility and Deviation Review Form for: ☐1 Pregnant Woman ☐2 Infant ☐3 Nursing Mother
3. Age (*in days*): ___ days
4. Date of birth *(if available)*: __/__/____ (DAY/MONTH/YEAR)
5. Sex: ☐1 Male ☐2 Female
6. If a Pregnant Woman, gestational age (*in weeks*): __ . _ weeks
7. If a Pregnant Woman, approximate or planned date of infant delivery: __/__/____ (DAY/MONTH/YEAR)
8. Last date to randomize (≤ 182 days from the date of birth) *(if applicable)*: __/__/____ (DAY/MONTH/YEAR)
9. Date of screening visit *(if applicable)*: __/__/____ (DAY/MONTH/YEAR)

C. ELIGIBILITY ISSUE DETAILS

1. Provide a brief description of the eligibility issue/deviation that requires review:

2. Provide a brief justification for the subject's enrollment into the study:

D. RELEVANT INFORMATION FROM STUDY DOCUMENTS

TNCC USE ONLY

1. Eligibility reviewed? Y N
   IF YES,
   a. Date of review: __/__/____ (DAY/MONTH/YEAR)
   b. Reviewer ☐1 TNCC ☐2 Committee Chair ☐3 Full Committee
   c. Eligibility decision: ☐1 Eligible ☐2 Not Eligible
   If NO,
   a. Reason not reviewed:
2. Comments:

Appendix E. Screening IDs

Clinic Name	Site Number	Screening Number Ranges
CHLA	4	61001-5 to 61100-7
Joslin Diabetes Center	8	61101-9 to 61200-0
University of Minnesota	9	61201-2 to 61300-5
UCSF	11	61301-7 to 61400-4
Indiana University	16	61401-1 to 61500-3
University of Iowa	198	61501-0 to 61600-2
The Children's Mercy Hospital	225	61601-4 to 61700-6
Utah Diabetes Center	502	61701-8 to 61800-1
CHOC	127	61801-3 to 61900-9

Screening ID Log for the NIP Diabetes Pilot Trial (XXXX)
Site:

Entry A:
The Pregnant Woman will receive the same Screening ID as their Infant. If there is a multiple birth, then designate the first Screening ID to the first born infant. The next available Screening ID will be given to the second infant.

Screening ID	Entry (A or B)	Pregnant Woman Name	Pregnant Woman Date Screened (DD/MMM/YYYY)	Preg. Woman Elig.?	Infant Name	Infant Date Screened (DD/MMM/YYYY)	Infant Elig.?	If Multiple Birth, First Born?	Comments

NIP Diabetes Pilot Schedule of Assessments

Timeline	Pregnant Woman during 3rd trimester Enters (A)			New Child Enters (B)	Follow-up Visits									
	Pregnant Woman Screening/ Enrollment	Infant Screening		Infant Screening 2 days to 5 mos of age	Infant Enrollment (4 wks after HLA blood collection)	Infant Age in Months								
		At Birth	2 to 28 days			3	6	9	12	15	18	21	24	q 6 mos
Informed Consent and HIPAA	P			Parent(s), I										
Medical History	P		I, N	I, N	I, M	N	I, N	N	I, N		I		I	I
Limited Physical Examination			I	I			I		I		I		I	I
Local HbA1c Screening[5]	P													
Local Blood Glucose Testing[4]							I		I		I		I	I
HLA Typing		I[cb]	I[2]	I[2]										
Islet Autoantibodies	P	I[cb]	I[2], M[A]	I[2], M			I		I[3]		I[3]		I[3]	I[3]
Tetanus antibody and cellular response									I					
Fatty Acids Analysis (RBC)	P	I[cb]			N[B], M[A]		I		I		I		I	I
Fatty Acids Analysis (breast milk)					N[B], M[A]	N	N	N	N					

P: Mother who entered her infant prenatally (she entered during pregnancy)
M: Mother (includes non-nursing and nursing mothers)
I: Infant
N: Nursing mother
Schedule of Assessments does not reflect when mother or infant attends the visit but what information is collected regarding mother and/or infant. Infants are not required to attend the infant enrollment visit, the 3, 9, 15, 21 month old visits, or every 6 months thereafter.
[A] Entry A: The mother entered during pregnancy
[B] Entry B: The infant entered after delivery
[cb] HLA typing on umbilical cord blood using an cord blood collection kit
[2] HLA typing and islet autoantibodies by heel stick for infants if umbilical cord blood was not obtained
[3] If 2 or more autoantibodies are present on or after the 12 month visit specimen, 1 to 2 months later a confirmation blood draw will be done. If the same 2 autoantibodies are present at both visits, the child will discontinue the study substance and withdraw from the study.
[4] If infant's blood glucose level is above 150 mg/dL the mother will be asked to do further tests, approx two hours after eating, and to provide these values to the local site.
[5] Local HbA1c screening will be done on pregnant mother if she has diabetes (Type 1, 2, or gestational)

Timeline (continued)	Pregnant Woman during 3rd trimester Enters (A)			New Child Enters (B)	Follow-up Visits									
	Pregnant Woman Screening/ Enrollment	Infant Screening		Infant Screening 2 days to 5 mos of age	Infant Enrollment (4 wks after HLA blood collection)	Infant Age in Months								
		At Birth	2 to 28 days			3	6	9	12	15	18	21	24	q 6 mos
Inflammatory mediators	P	I[cb]			N[B], M[A]		I		I		I		I	I
Vitamin D	P	I[cb]			N[B], M[A]		I		I		I		I	I
CRP	P	I[cb]			N[B], M[A]		I		I		I		I	I
Blood sample collected for storage													I	
Concomitant Medication Assessment (including vitamin and supplement)	P		M[A]	I, N	I, N[B], M[A]	I, N	I, N	I, N	I, N	I	I	I	I	I
Food Frequency Questionnaire	P		M[A]	N	N[B], M[A]	N	N	N	N					
Food Introduction History					I	I	I	I	I	I	I	I	I	I
Immunization Record					I		I		I		I		I	I
Provide DHA or Control (capsules or infant formula)	P		I, M[A]		I, N	I, N	I, N	I, N	I, N	I	I	I	I	I*
Adverse Events Assessments			I, M[A]		I, M[A]	I, N	I, N	I, N	I, N	I	I	I	I	I

P: Mother who entered her infant prenatally (she entered during pregnancy)
M: Mother (includes non-nursing and nursing mothers)
I: Infant
N: Nursing mother
***Up to 3 years of age**
[A] Entry A: The mother entered during pregnancy
[B] Entry B: The infant entered after delivery
Schedule of Assessments does not reflect when mother or infant attends the visit but what information is collected regarding mother and/or infant. Infants are not required to attend the infant enrollment visit or visits when they are 3, 9, 15, 21 months old.

Appendix H. Eligibility Reports

NIP Diabetes Pilot Trial

Entry A Infant Eligibility Report

V2. Report data as of: 0X/XXX/200X **Site Number: XXX**

Screening Number: XXXXX-X
Participant Letters: XXX
Date of Infant Delivery: 0XXXX200X

1. Participant Information

Date of birth: *XXXXXXXXX*
Date eligible infant must be randomized by: * *XXXXXXXXX*
Today's Age: XX *days*

2. Laboratory Results

Date HLA was collected: *XXXXXXXXX*
HLA risk: *Higher/Lower*

3. Biological Family History Information

Date NPP01 form completed: *XXXXXXXXX*
Mother: *Yes*
a. Father: .
b. Full sibling: .
c. Full sibling: .
d. Half sibling: .
e.1) If half sibling, infant shares biological: .
f. 1st degree relative of mother: .
g. 1st degree relative of father: .

Eligible based on HLA and Family History: Yes

* Note: Entry A Infant must be ≤ 28 days on the date of screening and ≤ 182 days on the date of randomization.

NIP Diabetes Pilot Trial

Infant Eligibility Report

Date as of: xx/xxx/xxxx (date)
Site Number: xxx (numeric)
Site Name: xxxxxx (alpha)
Screening ID: xxxxx.x (numeric)
Participant Letters: xxx (alpha)

Participant Information

Date of birth: xx/xxx/xxxx (date)
Date eligible infant must be randomized by (w/in 183 days): (date)
Gestational age at birth: xx weeks (numeric up to 2 digits)
Age: xxx days (numeric up to 3 digits)
Note: Gestational age of Infant at birth must be > 36 weeks.
Infant must be ≤183 days on the date of randomization.

Laboratory Results

Date HLA was collected: xx/xxx/xxxx (date)
HLA type: Higher risk or Lower risk
Protective allele: Present or Absent

NPP01 Infant's Type 1 Diabetes Biological Family History Information

Date Form Completed:

a. Mother: Yes or No
b. Father: Yes or No
c. Full sibling: Yes or No
d. Full sibling: Yes or No
e. Half sibling: Yes or No
    1) If half sibling, infant shares biological: Mother or Father
f. 1st degree relative of mother (her parent or sibling): Yes or No
g. 1st degree relative of father (his parent or sibling): Yes or No

Eligible based on HLA and Family History: Yes or No

Appendix I. EMINENT and Local Pharmacy Forms

Type 1 Diabetes TrialNet - NIP Pilot Trial (Protocol TN-06)

STUDY PRODUCT RETURN FORM

RETURN ONLY AGENTS SUPPLIED BY EMINENT SERVICES CORPORATION

The Agents listed below were returned by: _____

Address: _____

_____

_____

Site: _____

INSTRUCTIONS FOR INVESTIGATOR

1. Type or print clearly all information-one item per line. Fill in all sections.
2. DO NOT mark in the shaded area.
3. Sign and date list.
4. Pack the agents well to minimize breakage and leakage.
5. Enclose the completed list with the agents and return to:

Diabetes TrialNet - NIP Pilot Trial (0049)
c/o EMINENT Services Corporation
7495 New Technology Way
Frederick, MD 21703

Protocol No.	Agent Name	Strength & Dosage Form	Quantity	Lot #	For EMINENT USE only	
					Rec. Code	Checked by:
TN-06	DHASCO® -S 530 MG/ Placebo SGC, Gray					
TN-06	DHASCO® -S 530 MG/ Placebo SGC, Orange					
TN-06	DHASCO® -S 530 MG/ Placebo SGC, Red					
TN-06	DHASCO® -S 530 MG/ Placebo SGC, Yellow					
TN-06	Infant Formula, Gray 1 CAN					
TN-06	Infant Formula, Orange 1 CAN					Verified by:
TN-06	Infant Formula, Red 1 CAN					
TN-06	Infant Formula, Yellow 1 CAN					Date:

To be completed by site

Individual preparing this list:
(if other than the investigator)

_____ Name _____ Title

_____ Signature _____ Telephone No.

Comments: _____

0049_Ret_TN06 Rev 072706

EMINENT
SERVICES CORPORATION

CLINICAL SITE CONTACT INFORMATION

CLIENT ID #: 0049

Site # : _____ Protocol # : _____ New ( ) Change ( ) Delete ( )

Organization (Clinical Site):

Name	:			
Street Address	:			
City	:		State	:
Zip	:		Country	:
Tel	:		Fax	:
Web / Email:	:			

Consignee (Nurse/Pharmacist):

Name (F/M/L)	:			
Room /Suite #	:			
Department	:			
Tel	:		Fax	:
Email	:			

Investigator:

Name (F/M/L)	:			
Room/Suite #	:			
Department	:			
Tel	:		Fax	:
Email	:			
Street Address	:			
(If different from site)	:			
City	:		State	:
Zip	:		Country	:

Submitted by : _____ Date :

Approved by : _____ Date :

Implemented by : _____ Date :

Type 1 Diabetes TrialNet - NIP Pilot Trial (Protocol TN-06)

STUDY PRODUCT REQUEST FORM

Instructions: Type or print clearly all information except signature. Complete all sections except for box labeled For EMINENT Use Only. Sign the form in the space provided. All requests received by 2:00 PM EST weekdays will be shipped to arrive 2nd business day by 4:30 pm. Requests pertaining to refrigerated drug products will be shipped by Overnight Service to arrive by next business day 10.00 am. If Study product is needed overnight, check "Yes" in the Overnight field. If an overnight shipment is needed for Saturday and clinic personnel will be available to receive it, check "Yes" in the Saturday field.

FAX or Express Mail to:

EMINENT Services Corporation
7495 New Technology Way
Frederick, MD 21703

Phone: (240) 629-1972
FAX: (240) 629-3298

Clinical Investigator's Name:

Ordered by:

Telephone number: Site No.:

Date ordered: Date needed by:

Overnight: ( ) Yes Saturday: ( ) Yes

For EMINENT Use Only

Order # _____

EMINENT Sample #	Current Inventory	Agent Name	Unit	Quantity Required	Comments
		DHASCO® -S 530 MG/Placebo SGC, 100SGC/Bot, Gray	BOT		
		DHASCO® -S 530 MG/Placebo SGC, 100SGC/Bot, Orange	BOT		
		DHASCO® -S 530 MG/Placebo SGC, 100SGC/Bot, Red	BOT		
		DHASCO® -S 530 MG/Placebo SGC, 100SGC/Bot, Yellow	BOT		
		Infant Formula, Gray CAN, 6 CAN CASE	CASE		
		Infant Formula, Orange CAN, 6 CAN CASE	CASE		
		Infant Formula, Red CAN, 6 CAN CASE	CASE		
		Infant Formula, Yellow CAN, 6 CAN CASE	CASE		

TYPE Pharmacy shipping address below:
(No P.O. Box Numbers Please)

( ) Initial Request

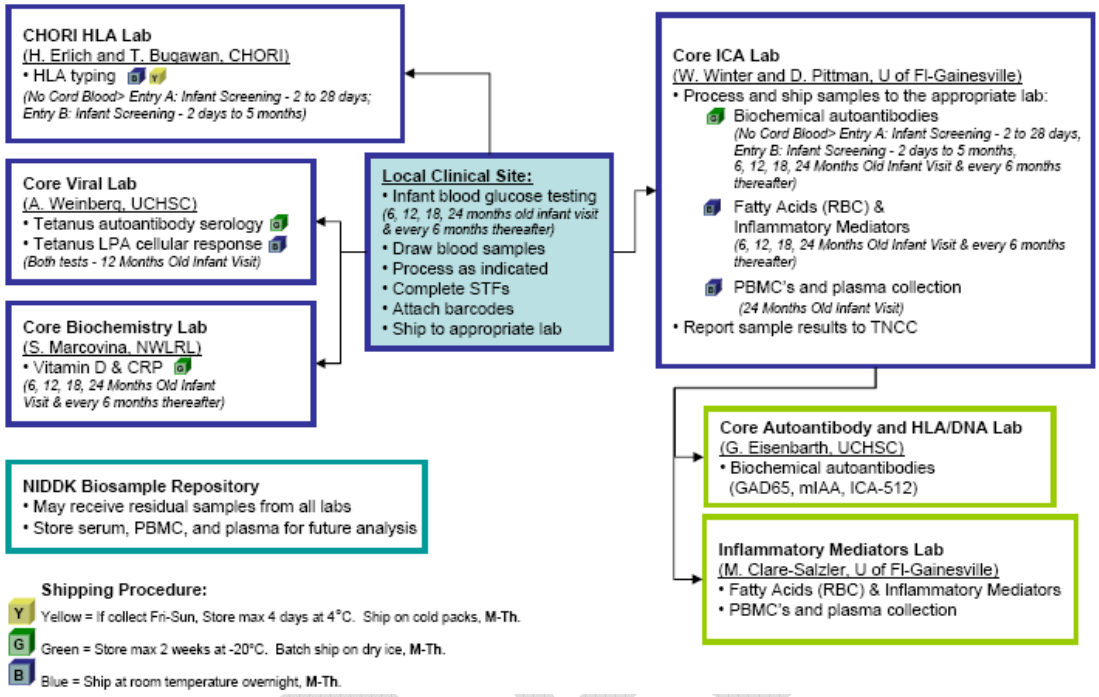
( ) Subsequent Request

_____ _____
Authorized Signature (Clinical Site) Date

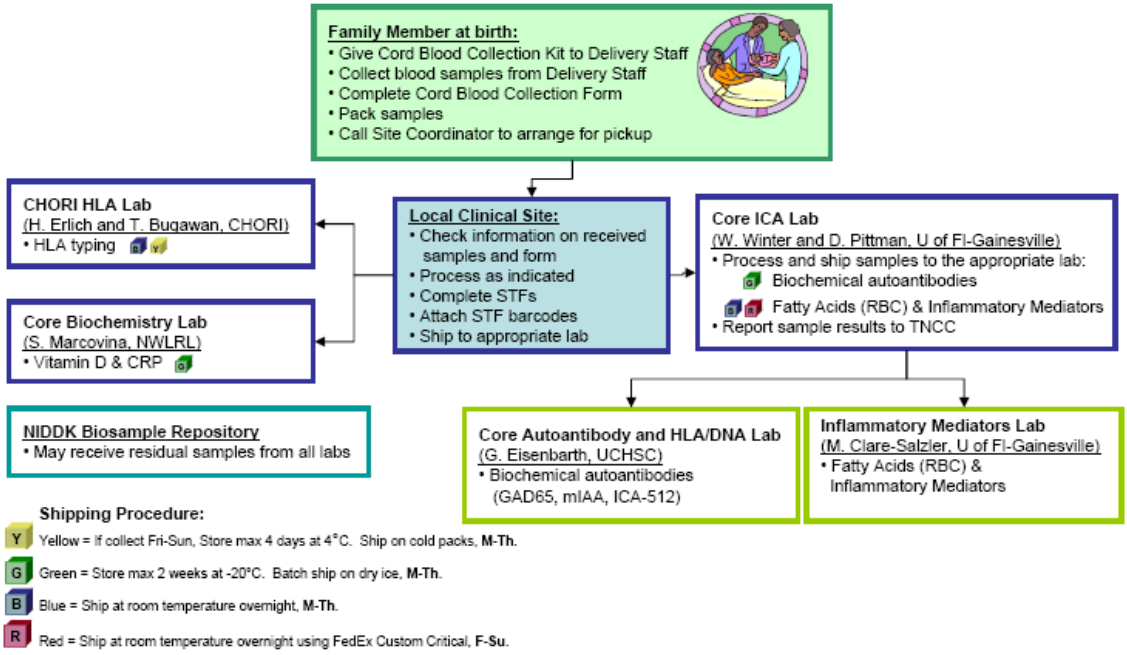
_____ _____
Authorized Signature (Client) Date

0049_Req_TN06 Rev.072706

Infant Specimen Flowchart

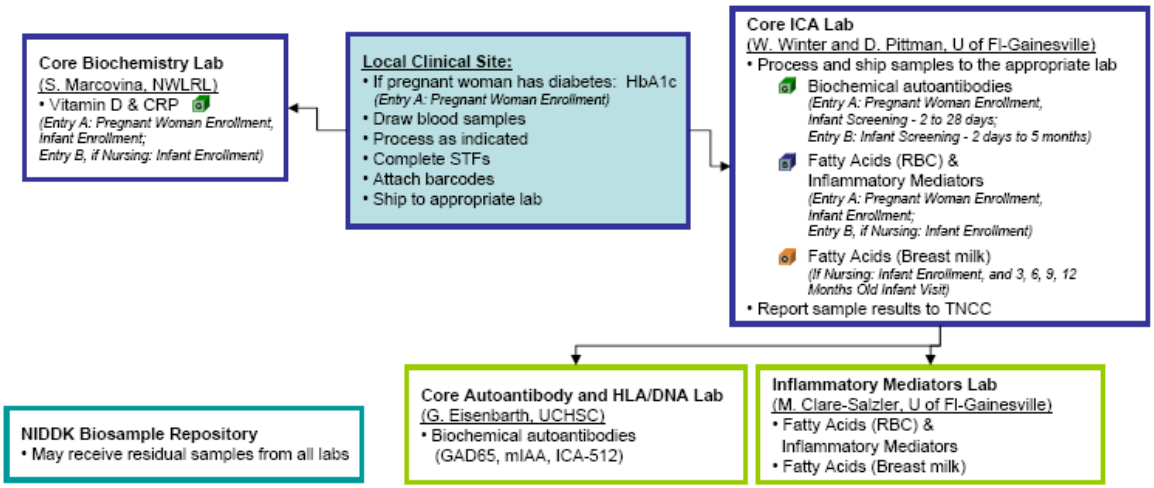


Cord Blood Collection Specimen Flowchart
Entry A: Infant Screening (at birth)



TrialNet NIP Diabetes Pilot Trial

Mother Specimen Flowchart



Shipping Procedure:

O Orange = Store overnight at -20°C. Ship on cold packs next day, **M-Th.**

G Green = Store max 2 weeks at -20°C. Batch ship on dry ice, **M-Th.**

B Blue = Ship at room temperature overnight, **M-Th.**