ISLET AFTER KIDNEY (CIT-06)

MANUAL OF PROCEDURES

VERSION 7.0

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CONFIDENTIAL

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Glossary of Abbreviations/Acronyms

AE	Adverse Event
BKV	BK Virus
BL	Baseline
cGCP	Current Good Clinical Practice
CGMS	Continuous Glucose Monitoring System®
CIT	Clinical Islet Transplantation
CITC	Clinical Islet Transplantation Consortium
CMV	Cytomegalovirus
CRO	Clinical Research Organization
CS	Clinically Significant
DCC	Data Coordinating Center
DDS	Diabetes Distress Scale
DSMB	Data Safety Monitoring Board
EBV	Epstein-Barr Virus
EC	Ethics Committee
eCRF	Electronic Case Report Form
EKG	Electrocardiogram
EQ-5D	European Quality of Life index
ES	Executive Secretary
FDA	Food and Drug Administration
FSIGT	Frequently-Sampled Intravenous Glucose Tolerance test
GFR	Glomerular Filtration Rate
HFS	Hypoglycemic Fear Survey
ICH	International Conference on Harmonization
ID	Identification
IIT	Intensive Insulin Therapy
IND	Investigational New Drug
IRB	Institutional Review Board
MAP	Mean Arterial Pressure
MMTT	Mixed Meal Tolerance Test
MOD	Magneto Optical Disk
MOP	Manual of Procedures
NCS	Not-clinically Significant

NIAID	National Institute of Allergy and Infectious Diseases
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
PC	Protocol Coordinator
PDT	Protocol Development Team
PI	Principal Investigator
PM	Project Manager
QC	Quality Control
QFT	QuantiFERON®-TB Gold test
QOL	Quality of Life
QST	Quantitative Sensory Testing
RC	Regulatory Coordinator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Study Coordinator
SF-36	SF-36 Health Survey
SOE	Schedule of Events
STS	Specimen Tracking System
TCAE	Terminology Criteria for Adverse Events
TB	Tuberculosis
TST	Tuberculin Skin Test
WL	Waitlist

1. Introduction

The study Manual of Procedures (MOP) is supplied to each participating site to aid in the conduct of the Clinical Islet Transplantation (CIT) Phase 3 protocol CIT-06. The purpose of this MOP is to provide guidelines and information that is not detailed in the protocol. These guidelines are designed to promote uniform performance of the trial across different institutional settings and to ensure excellent data quality.

All investigators and study staff should read the MOP before beginning subject recruitment and enrollment, and subsequently refer to it during the conduct of the trial. The current versions of the MOP and protocols are available on a web-site maintained by the Data Coordinating Center (DCC): *http://www.isletstudy.org*.

2. Study Organization

The Clinical Islet Transplantation Consortium (CITC) consists of numerous collaborating entities in an effort to conduct quality research protocols in the field of islet transplantation. In order to assist the site in identifying the appropriate individual to contact for questions or concerns throughout the study, a Communication Plan is provided in this Protocol-Specific MOP (see Appendix 20).

2.1 National Institutes of Health (NIH)

NIH is responsible for all scientific aspects of the study. The National Institute of Allergy and Infectious Diseases (NIAID) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) are accountable to higher levels of the Executive Branch, Congress and the public for the use of government funds. Please contact the assigned NIH Project Manager (NIH PM) for all protocol-related questions.

2.2 The DCC

The University of Iowa DCC provides statistical leadership for the development, implementation and analysis of CIT clinical trials. The DCC conducts data management and clinical trial quality control (QC), as well as supports regulatory and technical functions (*i.e.*, CIT website) and requirements associated with Investigational New Drug (IND) Applications and adverse event (AE) reporting. Additionally, the DCC conducts routine clinical site monitoring and will review data entry forms, source documentation, adherence to protocol requirements and submission of regulatory/clinical study documents as well as conducting training in protocol implementation.

2.3 Data Safety Monitoring Board (DSMB)

The DSMB provides independent review of data and safety monitoring procedures for all CIT protocols. The board meets to examine endpoint, toxicity, and safety data from NIAID/NIDDK-supported protocols. The DSMB may make recommendations concerning continuation, termination, or other modifications of studies based on the observed beneficial or adverse effects of any of the treatments under the study. The DSMB Charter is located in Appendix 1 of this manual.

3 Initial Institutional Review Board (IRB) /Ethics Committee (EC) Submission

3.1 Protocol Version Control, Finalization, and Approval Process

Protocol version control is extremely important, especially in multi-center trials, to ensure that all sites and all regulatory authorities receive identical documents. During protocol development, the NIDDK PM or the DCC PC maintains version control of the protocol documents. Before a protocol is considered "final" and labeled as Version 1.0, it must go through a formal review by the Protocol Development Team (PDT). The PDT consists of NIH clinical and regulatory staff, the Principal Investigator (PI) from each participating site and other designated site staff, and DCC staff. The NIDDK PM is responsible for obtaining all required approval signatures prior to finalizing the protocol document. Once the document is finalized, the NIDDK PM labels it as a whole version, e.g. Version 1.0, and distributes an electronic pdf version to all participating sites.

3.2 Consent Form Finalization and Approval Process

The CIT-06 study involves the use of two (2) consent forms. The first is the screening consent, which includes information about the screening, intensive insulin therapy (IIT) and waitlist (WL) procedures. The second consent is a transplant consent, which contains information specific to the islet transplant and subsequent post-transplant follow-up. The main contact for consent document finalization and approval is the NIDDK PM, who works to ensure collaboration and joint approval of all consent form documents.

Screening and transplant consent document templates are provided to all CIT sites by the NIDDK PM. Each site is responsible for inserting site-specific language into the templates. After the site-specific information is inserted into the consent documents, they must be reviewed by the NIDDK PM for inclusion of all essential elements and compliance with regulatory guidelines. Below is a set of instructions detailing the NIDDK review and approval process of the site-specific consent form(s). ***These steps must be completed prior to submitting any consent documents to the IRB/EC.***

1. The NIDDK PM provides the consent templates to the site for insertion of site-specific language.
2. The site modifies the consent templates as necessary and forwards them back to the NIDDK PM for review.
3. The NIDDK PM contacts the site within 5 business days with any comments/ suggestions or to provide approval of the documents.

Once the consent form(s) are approved by the NIDDK PM, an email notification documenting the approval for the specific consent version will be provided.

3.2.1 Translated Consents

Prior to IRB/EC review, the site is responsible for translation of the consent documents into the language appropriate for the potential consenting subject. The site should submit the translated consent forms to the DCC Protocol Coordinator (DCC PC) for back translation. The DCC PC will notify the NIDDK PM that the site submitted the translated consent documents, and will have the consent back translated using a certified translation service. The back-translated consent document will be forwarded to the NIDDK PM to review and verify that all elements of informed consent are addressed. All translation issues identified by the NIDDK PM must be addressed before IRB/EC submission. This process may take up to 2 weeks to complete.

3.3 NIH Authorization to Submit to the IRB/EC

Once the protocol is finalized and the informed consent document(s) have been approved by the NIDDK PM, the site will receive a memo with instructions that they may proceed with submission to the IRB/EC. Only protocol documents and consent forms indicated in this authorization memo should be submitted to the IRB/EC.

The same process utilized for the initial protocol/consent submission is also followed for protocol amendments and any subsequent changes to the consent form(s), including modifications requested by the IRB/EC after initial submission. Please contact the NIDDK PM with any questions or concerns regarding the processes outlined above.

4 Regulatory/Clinical Study Document Collection

After the NIDDK PM has provided authorization for the site to submit version 1.0 of the protocol and consents to the IRB/EC, the site will receive a Regulatory/Clinical Study Document Binder and an associated instruction memo from the DCC PC. The site is responsible for submitting all required regulatory and clinical study documents to the DCC, as instructed in the memo and described on the tabs within the Regulatory Document Binder. It is ideal that all required regulatory and clinical study documents be submitted to the DCC prior to scheduling the site initiation visit.

5 Site Training and Monitoring

Prior to beginning subject enrollment and throughout the duration of the study, the site staff will receive study-specific training performed by the NIH and DCC staff. Site training is accomplished through a site initiation visit, interim monitoring visits, protocol review calls, other ad-hoc training calls or visits as needed, and a final site close-out visit.

5.1 Site Initiation Visit

The site initiation visit will be performed by the NIDDK PM, the DCC PC, and the DCC RC. Additional NIH or DCC staff may be invited to attend the visit to provide ancillary training or serve as observers. The site initiation visit will include training on the CIT-06 protocol and will include discussions on the following topics:

- Investigator and Staff Qualifications and Responsibilities
- Protocol and Study Design
- Facility and Equipment Review
- Electronic Case Report Form (eCRF) Completion, Data Entry System, and CIT Website
- Documentation Procedures and Requirements (including source documentation and proper maintenance of regulatory and clinical study documents)
- Investigational Product (if applicable) and Study Supplies Ordering and Accountability Procedures
- Current Good Clinical Practice (cGCP) and International Conference on Harmonization (ICH) Guidelines
- Serious Adverse Event (SAE) Reporting
- Laboratory Procedures (including specimen collection, storage, and tracking)

5.2 Site Activation

Before a site may begin enrolling subjects in the CIT-06 study, the site must be activated by the NIDDK PM. The NIDDK PM will provide a Site Activation Letter to the PI and Study Coordinator (SC) after the following have been completed:

- The site has obtained IRB approval for the protocols and NIH-approved consents;
- All required regulatory and clinical study documents have been submitted to the DCC; and
- The site initiation visit has been completed and all outstanding issues from that visit have been resolved.

5.3 Interim Monitoring Visits

Routine monitoring visits for all CIT protocols will be conducted by a DCC Protocol Coordinator. The frequency of these visits will vary depending on protocol compliance and rate of subject recruitment. A DCC Protocol Coordinator will contact the site staff directly to schedule interim monitoring visits; any questions or concerns regarding the conduct of the visit should be addressed to the NIDDK PM.

The purpose of interim monitoring visits is to ensure compliance with regulatory requirements and study procedures. Interim monitoring visits will involve a review of clinic, laboratory and pharmacy (if applicable) operations. Specifically, the protocol coordinator conducting the monitoring visit will verify source documentation against data entered in the database, perform drug accountability checks (if applicable), review regulatory/clinical study document binders, provide additional GCP/ICH training as necessary, and discuss pertinent study implementation issues. The SC, PI, and Pharmacist must be available to meet with the protocol coordinator during the conduct of these visits.

At the end of each interim monitoring visit, a summary meeting will be held with the PI and SC to review any pertinent findings and items requiring follow-up action. A formal letter, including outstanding action items and a summary of the monitoring visit, will be sent to the site within 3 weeks of the visit, and a copy will be provided to the NIDDK PM. Once all action items from the visit have been resolved, the DCC will send a signed hard copy Site Interim Monitoring Post-visit Follow-up Letter to the PI and SC and request that the site place a copy of the letter into the Site Regulatory Binder.

5.4 Protocol Review Calls

The NIDDK PM and/or the DCC PC will conduct scheduled conference calls with the site SCs, as needed, to facilitate communication among the sites. Discussion may include:

- Enrollment procedures
- Recruitment strategies
- Data quality compliance *(i.e.*, eCRF completion)
- Study procedures/Updated study information

5.5 Close-out Visit

The DCC will conduct a final close-out visit after the study is completed and all data are submitted to the DCC and have been monitored. During the close-out visit, a DCC representative will review regulatory requirements for maintaining records and ensure the return or destruction of all unused investigational products or study supplies. After the visit, a final letter indicating the completion of the study will be sent to the sites, and a copy will be provided to the NIDDK PM. Each site is responsible for notifying the IRB/EC of the completion of the study.

6 Enrollment, Screening, IIT, WL, Baseline (BL), and Transplant

6.1 Enrollment

When a potential subject appears to have met general study eligibility criteria, he/she may be approached regarding participation in the CIT studies. After he/she signs the IRB/EC and NIH-approved screening consent document, he/she is considered enrolled in the CIT protocol (CIT-06). Each subject should be given adequate time to read the screening consent and must sign the screening consent prior to undergoing any study-specific screening procedures.

The consent process must include a detailed summary of the study and answers to any questions raised by the potential subject. Only after the PI or delegated study staff is assured that the subject and/or legal guardian understands potential risks and benefits of participation in the studies should written consent be obtained. If there are any changes to the protocol(s) that require modifications to the consent form, each subject must sign a new version of each consent form, depending on the subject's timeline in the study.

The original signed screening consent form should be placed in the subject's research file, and a copy of the signed document should be provided to the subject and/or legal guardian. In addition, a progress note confirming the following should be added to the subject's medical record:

- subject's questions were answered
- subject received a copy of the consent
- subject met all of the inclusion/exclusion criteria
- subject signed the enrollment consent

All subjects who sign the screening consent should be officially enrolled in the study using the DCC electronic data entry system. To do this, study staff must complete the *Informed Consent* eCRF by first clicking "Enroll New Subject", accessible under the CIT Menu "Data Collection" and "IAK 06 Subject Data" link. Once the date on which the screening consent was signed is entered and the *Informed Consent* eCRF is "submitted", the computer will generate a CIT Subject Identification (ID) number. The Subject ID will consist of a leading "06" (indicating CIT-06), followed by the Site # and then three (3) additional numbers. Before screening can begin, study staff must also complete the *Demograhpic* eCRF found in Visit 1.

6.1.1 Subject ID Number

The unique Subject ID Number is 7 characters in length and unique to each subject. The format of the unique Subject ID Number is as follows:

0X – NN – NNN

The number is broken down as follows:

- 0X = the protocol number to which the subject was enrolled
- NN = 2 digit code for the Site-ID number
- NNN = 3-digit number assigned sequentially based on site enrollment

6.2 Screening

After the subject is enrolled, as documented by signing the screening consent, he/she will undergo CIT-06 specific screening procedures to determine eligibility. If the potential subject has information available from his/her standard medical care that is current, this data may be used to determine eligibility. (Note: The screening physical examination must be conducted and/or signed off by an investigator listed on the site's 1572 form.) Tests conducted within the time window identified in the SOE for the wait list visit (03) are considered current for screening purposes. Please see Section 7.1 (Enrollment and Screening) of the CIT-06 protocol for more information on timeframes for screening assessments.

The following schematic describes the order in which screening assessments should be completed in order to determine eligibility for the CIT-06 study.

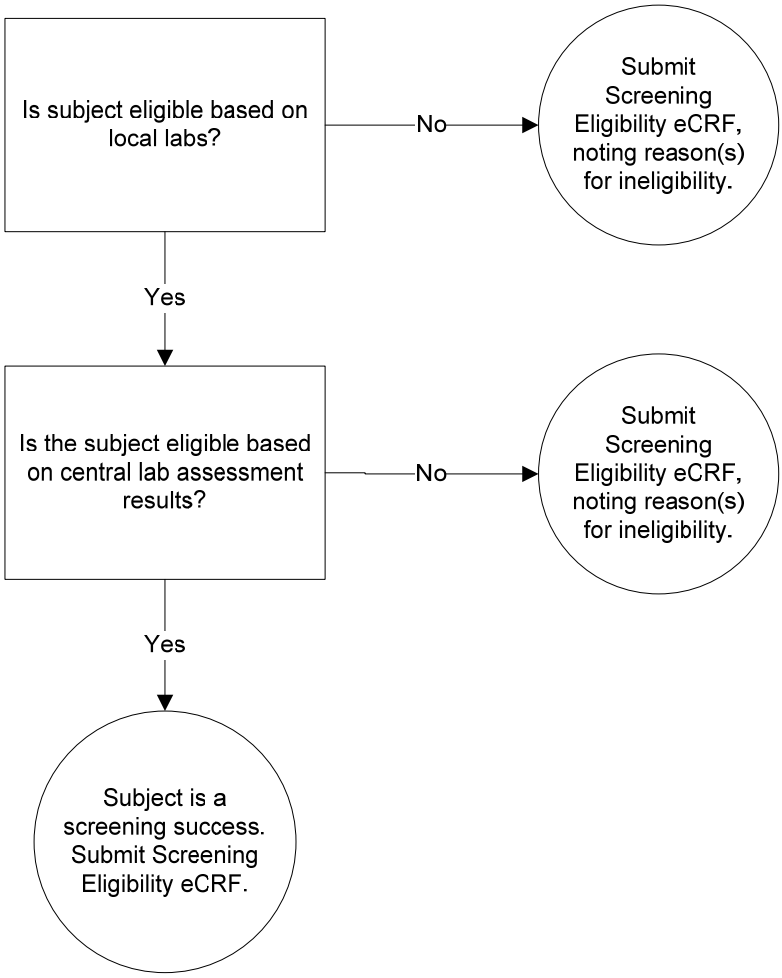


Figure 1: Determining eligibility in CIT-06 study

Once it is confirmed that a subject meets all screening eligibility criteria, he/she is considered screened eligible. The site should complete the Screening Eligibility eCRF at this time. Completion of the Screening Eligibility eCRF with successful screening results signifies that the

subject is eligible for the CIT-06 protocol; s/he is not necessarily eligible for a transplant at this point.

6.3 Intensive Insulin Therapy

Each subject must complete a period of IIT prior to islet transplantation, either 1) in the 12 months prior to enrollment, or 2) between enrollment and islet transplantation.

1. **CIT06 protocol, Inclusion Criterion #7, Option 1, page 8** Some subjects may have received intensive diabetes management prior to enrolling in the study. These subjects must demonstrate the following to meet this inclusion criterion:

    a. Self monitoring of glucose values no less than a mean of three times each day averaged over each week and by the administration of three or more insulin injections each day or insulin pump therapy (CIT06 protocol, section Study Definitions, page 21); and

    b. Intensive diabetes management under the direction of an endocrinologist, diabetologist, or diabetes specialist with at least 3 clinical evaluations during the 12 months prior to study enrollment.

Study tools are provided in Appendix 2, Determining Eligibility Instructions and MD Referral Letter, and Appendix 3, the Diabetes Specialist Questionnaire. In addition, the Clarke score must be evaluated at the time of enrollment and must be greater than or equal to 4 for eligibility.

Subjects who meet this criterion option do not need to initiate the study-directed IIT portrayed as Visit 02 on the SOE. These subjects may be listed to the protocol waitlist, and are expected to continue their intensive diabetes management while waiting for an islet transplant.

2. **CIT06 protocol, Inclusion Criterion #7, Option 2, page 8** Subjects who do not meet the requirements for IIT prior to enrollment must initiate the therapy while enrolled in the study. This period of IIT is portrayed in the SOE as Visit 02, IIT and continues for at least 4 months, but up to 12 months. If at any time between 4 months and 12 months of IIT while on study the subject has both a Clarke score of 4 or more AND at least 1 episode of severe hypoglycemia, the subject will be considered eligible for the protocol's waitlist. See Appendix 3 of the protocol for more information about Diabetes Management and Education.

3. **CIT06 protocol, Inclusion Criterion #7, Option 3, pages 8-9** If after 12 months of IIT the subject does not exhibit reduced awareness of hypoglycemia (i.e. does not meet Options 1 or 2), the subject may be eligible for the protocol's waitlist if the HbA1c is $\geq$ 7.5% and it isn't more than 0.1% lower than the preceding month. Two examples are provided:

    a. **ELIGIBLE:** Monthly HbA1c values 9.7%, 9.5%, 9.4%, 9.4%

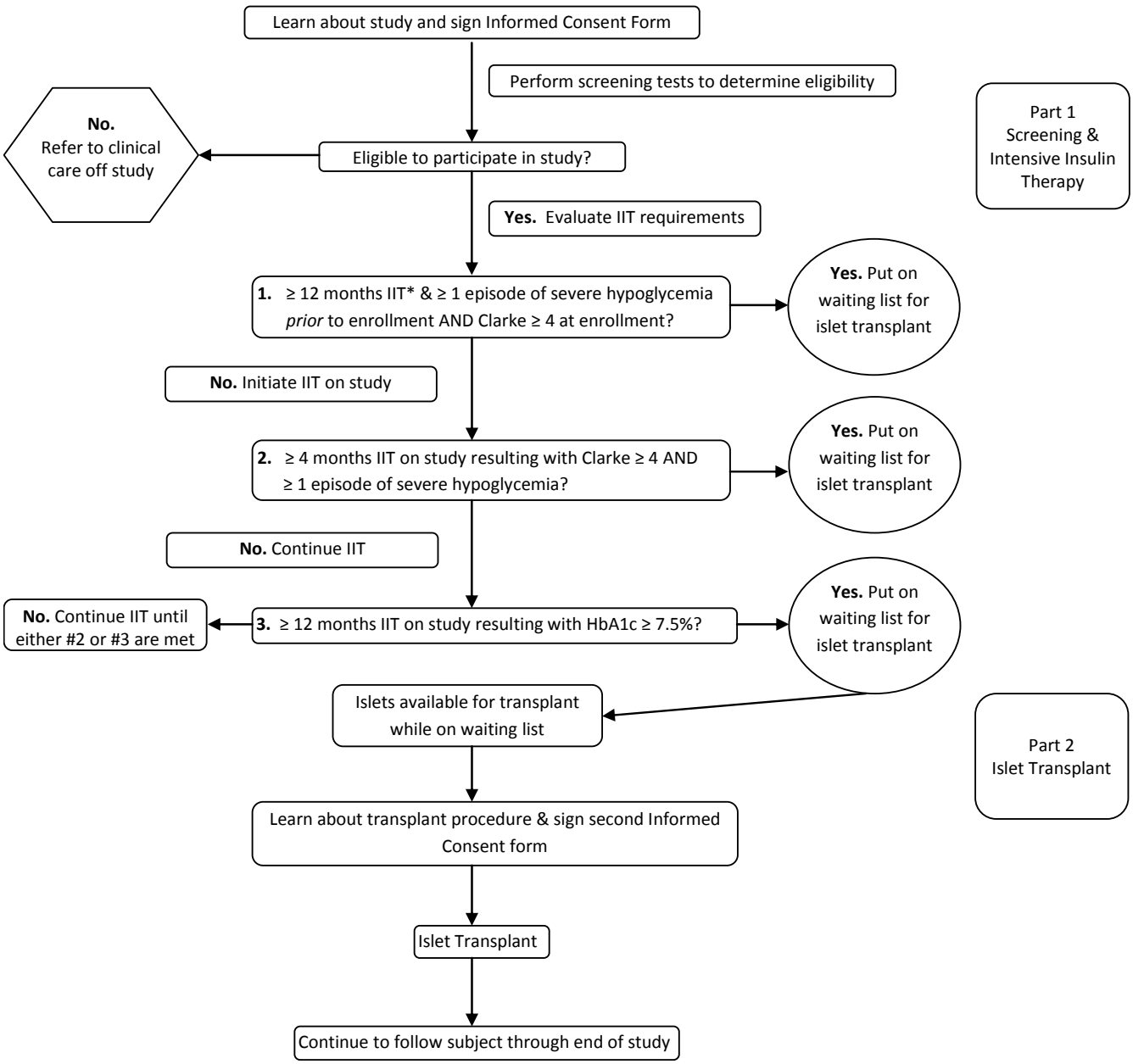
    b. **INELIGIBLE** (for this option only): Monthly HbA1c values 8.2%, 8.0%, 7.9%, 7.7%

4. **CIT06 protocol, Inclusion Criterion #7, Option 4, page 9** If after 12 months of IIT the subject does not exhibit reduced awareness of hypoglycemia (i.e. does not meet Option 2) and the HbA1c is not yet stable (i.e. does not meet Option 3), then the subject may continue IIT while being enrolled in the study until either:

    a. **Option 2 is met:** Clarke score of 4 or more AND at least 1 episode of severe hypoglycemia; OR

    b. **Option 3 is met:** HbA1c is ≥ 7.5% and it isn't more than 0.1% lower than the preceding month.

Figure 2: Inclusion #7 Eligibility Flowchart



** IIT prior to enrollment is the same as intensive diabetes management under the care of a diabetes specialist. Blood glucose must have been tested an average of three times each day. In addition, insulin must have been taken at least three times each day. Insulin pump therapy is allowed.*

Most of the assessments listed in the IIT column (Visit 02) of the SOE are conducted only once (marked by a stand-alone "X" on the SOE, *e.g.* Chemistry) during the minimum 4 months of structured IIT. These results should be recorded on the appropriate Visit 02 eCRFs.

The frequency of any repeat assessment is indicated next to the "X" for that particular assessment. For example, HbA1c is listed as "X-q1mo"; therefore, all subjects must have blood drawn locally each month while in IIT and on the waiting list.

6.4 Waiting List

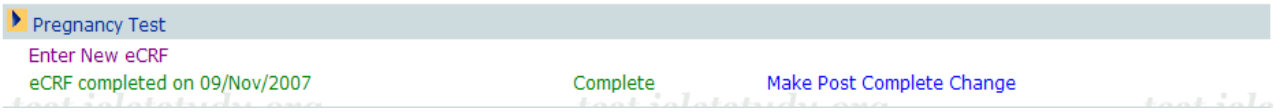
The Waiting List (WL - Visit 03) on the SOE begins after the subject has completed at least 4 months of IIT and continues until Day -2. A subject's IIT care continues during this time.

There are two aspects to the WL visit in CIT-06: the *protocol* waitlist and listing a subject on the UNOS waitlist. Once a subject meets the IIT inclusion criterion, s/he can be said to be on the protocol waitlist, and all of the assessments listed in the WL column of the protocol SOE must be completed or repeated if out of window. Assessments with a single X in the WL column must be completed at this time, even if the screening assessment as conducted just a week prior. Assessments with a frequency attached to the X (e.g., X-q3mo) must be completed for the first time if not already done during screening (e.g. local PRA), or frequency assessments must be repeated if the time between the screening assessment and the transplant is expected to be greater than the frequency noted. Once all WL assessments listed in the SOE have either been performed or verified within window, ***and*** the results have been received, those results should be reviewed for transplant eligibility, and if eligible, then activated on UNOS. A subject cannot be listed as active on the UNOS waitlist until the site has a complete set of within-window results that satisfy the CIT-06 inclusion/exclusion criteria.

WL assessments that are conducted only once (marked by a stand-alone "X" on the SOE) should be scheduled when it is convenient for the subject to return based on the need for repeat assessments. All WL assessments must be conducted and the results received and evaluated by the clinical site prior to the start of induction immunosuppression. The results from these tests are considered BL results that will be used to reconfirm eligibility prior to transplant. These results should be recorded on the corresponding Visit 03 eCRFs.

Most of the assessments listed in the WL column of the SOE must be repeated. The frequency of each repeat assessment is indicated next to the "X" for that particular assessment. For example, Local PRA is listed as "X-q3mo"; therefore, all subjects must have blood drawn every three months while on the waiting list. If a subject misses a repeat assessment (*e.g*. quarterly QOL, etc) it is considered a minor deviation. All efforts should be made to assure the subject is seen at the clinical site as soon as possible to complete the repeat assessments. If the subject has still not been seen by the 6 month visit, the subject should be inactivated on the UNOS transplant list until the repeat assessments can be completed in order to confirm transplant eligibility.

The results of each repeat assessment should be entered into the corresponding Visit 03 eCRFs. For example, a pregnancy test must be conducted yearly, according to the SOE. When an initial pregnancy test is conducted and the results are entered into the *Pregnancy* eCRF, a second Pregnancy eCRF will become available (see below). Within the eCRF listing in the CIT database, you will see the completed eCRF (November 9, 2007) and a link to add a new *Pregnancy* eCRF one year later ("Enter New eCRF").



If the subject fails a repeat test while on WL and the investigator believes that the cause of the failure is a transient condition, the subject can stay on WL and be re-tested according to the SOE. However, while the subject's lab values are out of normal range, his/her status on the UNOS waitlist should be changed to "inactive". The subject's status can be changed back to "active" when s/he once again meets the protocol eligibility criteria. At this time, any out-of-window WL/BL assessments must be updated. All lab values and assessments must be within window and within the limits of the inclusion/exclusion criteria at the time of transplant.

Notes on PRA: If a subject has a PRA that does not meet the inclusion/exclusion criteria, s/he must be terminated from the study. The site must have a set of PRA results from the waitlist visit before a subject can be made eligible on the UNOS waitlist. Local PRA must be collected and analyzed every 3 months, but only a single central PRA result is required prior to putting the subject on the UNOS waitlist.

Subjects who become ineligible while on WL/BL should be terminated from the study. Please see Section 11.2 for details on how to terminate a CIT subject.

6.5 Baseline

The Baseline (BL - Visit 04) on the SOE begins on Day -2 prior to induction immunosuppression for the islets.

Once a suitable islet preparation becomes available, WL subjects having a blood type compatible with the pancreatic donor and crossmatch negative (performed on banked serum ≤ 30 days prior to transplant) will be selected. Continued eligibility should be reviewed based on the most current wait list data obtained.

BL assessments are conducted only once (marked by a stand-alone "X" on the SOE) and should be completed prior to induction immunosuppression AND within two days prior to islet transplantation. Results should be recorded on corresponding Visit 04 eCRFs.

As soon as a subject is considered eligible for the transplantation, he/she should be consented using the transplantation IRB/EC and NIH-approved consent form. The transplantation consent process must include all of the elements described for the enrollment consent (see section 6.1). In addition, site personnel should provide the subject with a copy of the enrollment s/he signed most recently so that the subject can review it along with the transplantation informed consent. The original signed transplant consent form should be placed in the subject's research file, and a copy of the signed document should be provided to the subject and/or legal guardian. A progress note confirming the following should also be added to the subject's medical record:

- subject's questions were answered
- subject received a copy of the transplant consent

- subject received a copy of the most recently signed enrollment consent to review
- subject met all of the inclusion/exclusion criteria
- subject signed the transplant consent

6.6 Islet Transplantation

Once a suitable islet preparation becomes available, WL subjects having a blood type compatible with the pancreatic donor and crossmatch negative (performed on banked serum ≤ 30 days prior to transplant) will be selected. Continued eligibility should be reviewed based on the most current wait list data obtained.

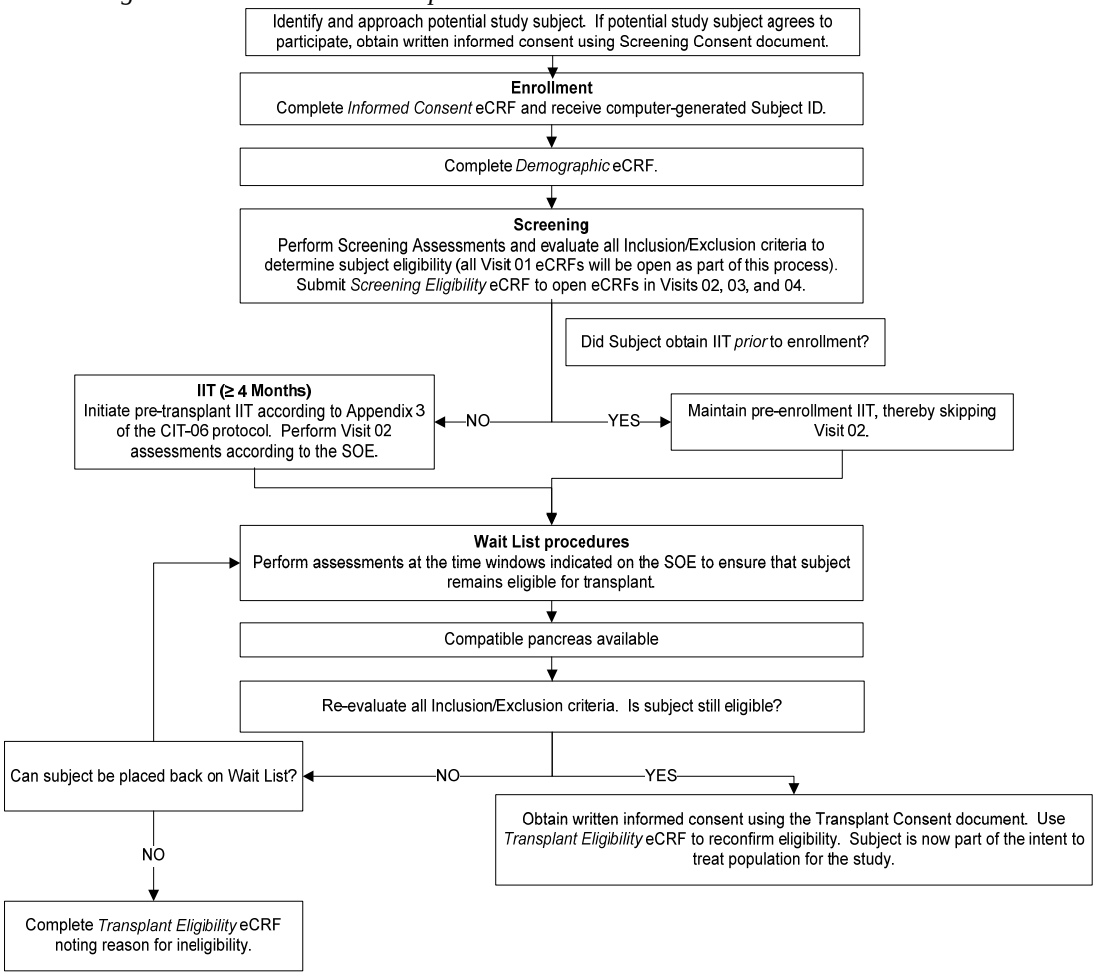
Eligibility must be reconfirmed by completing the *Transplant Eligibility* eCRF. If the subject is no longer eligible, the site should access the *Transplant Eligibility* eCRF and mark all known reasons for ineligibility. Once the form is "submitted", the subject is automatically excluded from the study, and no further data is collected.

If the subject is confirmed to be eligible for transplant, the site should access the *Transplant Eligibility* eCRF, complete and "submit" the form. This form must be submitted before the islet transplant takes place. Once the form is submitted, the system will display a prompt that confirms the intent to transplant the subject.

What if induction immunosuppression has been initiated, and then the islet preparation fails? If the repeat crossmatch or failure of the islets makes the subject unable to receive the islet transplant, the subject will be given priority status for the next available set of islets.

What if the islets fail prior to the administration of the induction immunosuppression*?* If the islets fail before the subject is given the induction immunosuppression, a subject meeting transplant eligibility criteria may be placed back on the waiting list.

Figure 3: Enrollment & Transplant Flowchart



7 Instructions for Study-Specific Procedures

7.1 Central Laboratory Tests and the Specimen Tracking System (STS)

Each of the CIT protocols will have some tests submitted to central laboratories. The table below represents a comprehensive list that will be submitted to central laboratories for processing.

Table 1: Central laboratory assessments

Test	Central laboratory
Mixed-meal tolerance test (MMTT)	University of Washington
HbA1c	University of Washington
Fasting serum glucose and c-peptide/ creatinine	University of Washington
Atherogenic profile	University of Washington
Insulin-modified frequently-sampled intravenous glucose tolerance test (FSIGT)	University of Washington
Alloantibodies	University of Pennsylvania
Autoantibodies	Barbara Davis Center
Plasma to archive	NIDDK Repository
Albumin/creatinine ratio	University of Minnesota

CIT employs a STS to assist staff in collecting, processing, shipping and tracking these centrally-analyzed samples.

7.2 HLA Antibody Screening and PRA

7.2.1 Methodology.

For the CIT consortium project, solid phase luminex bead assays are used for anti-HLA antibody detection and characterization. The luminex technology has a very high level of sensitivity for detection of antibodies, and computer software allows the user to view data in different formats to assist in the analysis (creg groups, antigen vs. allele level analysis).

Subject sera are screened for the presence of anti-HLA class I and class II antibodies using the Luminex Mixed bead assays. Positive relativities observed in the Luminex Mixed bead assays will be confirmed by Luminex Specificity and in selected cases, with Luminex Single Antigen bead assays as shown in the flow chart in Section 7.2.5.

7.2.2 Interpretation of test results and decision algorithm for islet cell transplant candidates during the pre-transplant period.

It is critical to delineate true weak reactivity to HLA alloantigens from non-specific binding which can be occasionally observed in some subjects' sera using these assays. Thus, ambiguous results and weak reactivity are further evaluated by comparing results obtained in 3 different Luminex-based assays (Mixed Beads, Specificity Beads and Single Antigen Beads). Weak reactivity using the Luminex Specificity beads assay is defined by fluorescence intensity with MFI values in the range of 1000-3000. Moreover, the intensity of fluorescence, the pattern of serum reactivity and its consistency are taken into account in the interpretation of the test results. The combination of these assays should provide a complete identification of HLA specificities. Transplant candidates that demonstrate weak to moderate reactivity with MFI values in the range of 1000-6000 may require repeat testing after 1-2 months period to confirm the presence of the detected antibodies and their specificity. The decision to request a new sample for repeat testing will be made in consultation with the transplant center taking into account the history of sensitization (pregnancies and transfusions). This approach should provide more confidence that examples of weak reactivity represent true positives; in this manner we hope to minimize the exclusion of subjects with false positive results. A decision algorithm for subjects' inclusion and exclusion is described in the attached flow chart.

7.2.3 Reports of test results

All reports will include antibody specificity and a recommendation for subject eligibility to enroll in the study. In selected cases, additional information or consultation with the transplant center may be needed to determine eligibility.

The sensitivities and specificities identified by the University of Pennsylvania HLA lab may be different from those identified at sites' local labs. Therefore, potential subjects should not be screened out of the CIT studies on the basis of local PRA/HLA assessments.

If a subject is weakly positive (has a positive PRA) for some antibodies but the antigens/specificities can be identified, the Penn HLA lab may recommend that s/he can be enrolled in the CIT studies with PI permission, as long as the identified antigens are avoided when the subject is transplanted.

7.2.4 CIT-06 Exclusion #8 PRA Clarification

Clarification is provided below in bold to further interpret eligibility for the initial transplant.

"Calculated panel-reactive anti-HLA antibodies > 50%. Subjects with calculated reactive anti-HLA antibodies ≤50% will be excluded if any of the following are detected:

a. Positive cross-match **(Positive flow T cell or B cell cross-match due to donor-directed Class I or Class II anti-HLA antibodies. Donors with positive flow B cell crossmatches that may be due to autoantibodies or Non-HLA antibodies should not be excluded),** or

b. Islet donor-directed anti-HLA antibodies detected by Luminex Single Antigen/specificity bead assay including weakly reactive antibodies **(MFI values in the range of 1000-3000)** that would not be detected by a flow cross-match

Note the following:

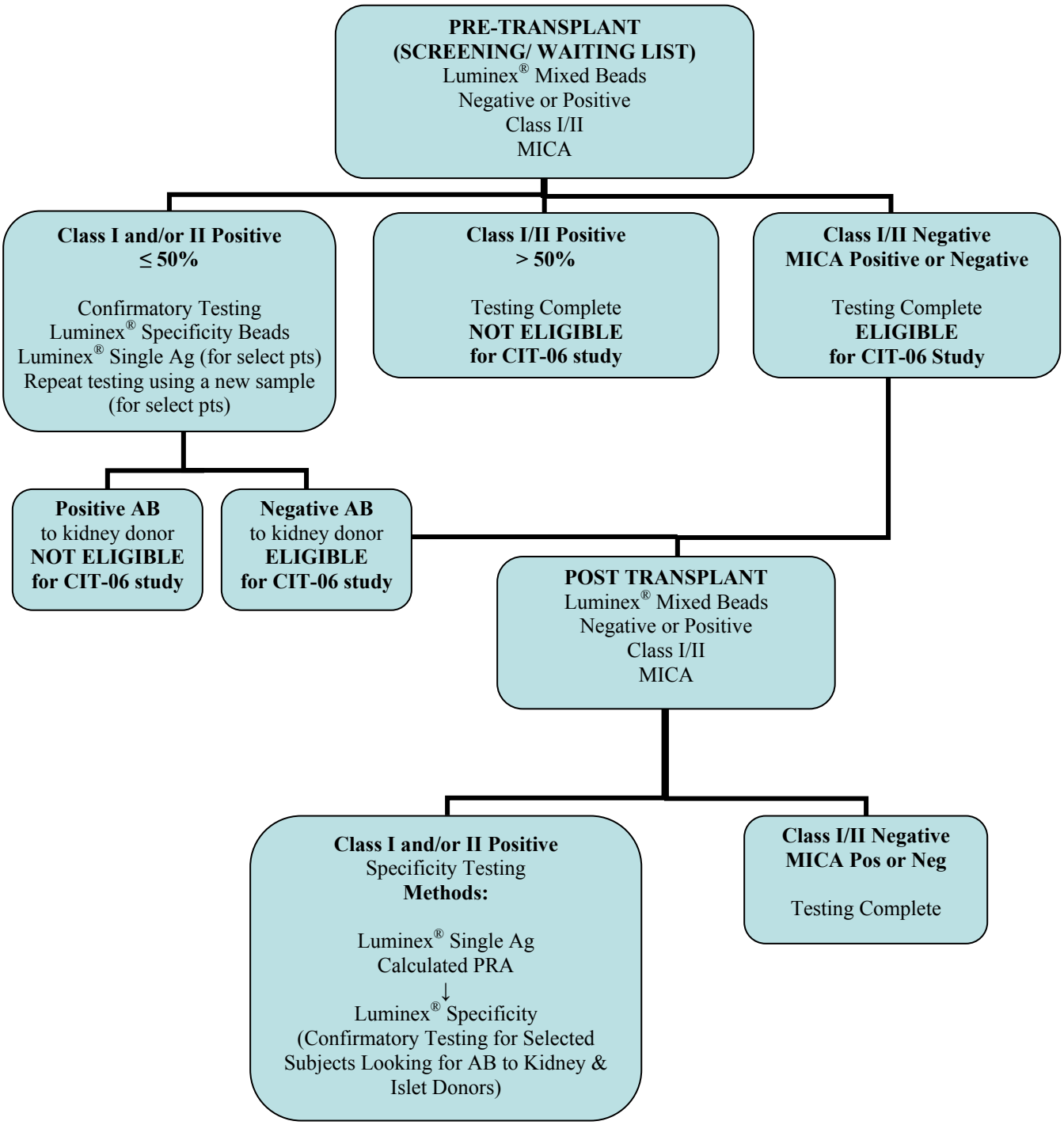
i. Donor HLA class 1 (HLA-A, B, Cw) or HLA class II (DR, DQB) antigens should be identified by all typing laboratories, but
ii. Donor HLA class II (HLA DQA, DP) or HLA allele-specific antibodies may NOT be identified by all typing laboratories.

If anti HLA antibodies are detected in the potential islet recipient to ANY of the above antigen classes, an islet donor cannot be used for that patient unless the donor is KNOWN to lack the antigen. If the initial typing report for the islet donor does not include testing for all antigens to which antibodies are found in the recipient and the donor cannot be typed in a timely fashion for these specificities, that donor cannot be used for that recipient. or

c. Antibodies to the renal donor (i.e. presumed denovo). **Class I or Class II anti-HLA antibodies will be identified by the Luminex Single Antigen Assay.**

In some cases, HLA antibodies found in the potential islet recipient may be directed to HLA-DQA, HLA-DP or HLA class I or class II alleles. In these cases the HLA lab will request additional HLA typing information on the kidney donor. This additional typing information may need to include HLA typing of HLA-DQA, DP or allele level typing."

7.2.5 HLA Antibody Screening Flow Chart and Decision Algorithm



7.3 Epstein-Barr Virus/Cytomegalovirus/BKV Monitoring Algorithm

Cytomegalovirus (CMV) viral load in plasma will be measured at baseline prior to islet transplantation. Any value >500 copies/mL of plasma is considered positive for active viremia. CMV monitoring should occur as specified in the CIT-06 SOE. Three to five fold differences in quantitative viral load assessment may represent precision variability within the assay and should not be considered CS. Particular concern should occur if a rise greater than fivefold over baseline occurs within one week or if the quantitative level at baseline is >25,000 copies/mL. Management of a CMV viremia will be in accordance with the standard of practice at the local institution with appropriate infectious disease consultation support. International guidelines for subject management may be useful to guide intervention in this setting[2].

Epstein-Barr Virus (EBV) viral load assessments in whole blood will be measured as specified in the CIT-06 SOE. The assay does not detect latency and detectable quantitative loads in whole blood represent evidence of EBV reactivation. If EBV DNA is detected in whole blood at any time at a level higher than the threshold for detection at the relevant laboratory, the frequency of monitoring should be increased to weekly and continued until two consecutive negative results are obtained. Three- to five-fold differences in quantitative viral load assessment may represent precision variability within the assay and should not be considered CS. In subjects who are EBV seropositive before transplant, asymptomatic EBV reactivation with levels measurable in whole blood is not uncommon and is usually self-limited, requiring no intervention. Particular concern should occur if a rise greater than five-fold over baseline occurs within one week. Many laboratories will have an absolute level indicative of concern even if detected at baseline. Infectious Disease consultation should be sought to assist in further management in these settings. Management of an EBV reactivation will be in accordance with the standard of practice at the local institution. International guidelines for subject management may be useful to guide intervention in this setting[3].

BK viral load in urine or plasma will be measured as specified in the SOE for the CIT-06 protocol. Urine and/or plasma samples will be screened for each timepoint.

Upon screening for the study, if viremia is detected, the subject will be excluded from further participation in this protocol. Urine will also be collected at the time of transplant and at the time of any subsequent islet transplant. The results of this screen will not be available to the clinical centers prior to the islet transplant, but these results will be returned to the center investigator to be used as per the investigator's judgment and in accordance with standard practice.

All further testing for BK virus (BKV) will be "for cause," i.e., in accordance with standard practice. For instance, in the event of a rise in serum creatinine levels (>25% over baseline), persisting after correcting for obvious clinical issues (dehydration, high calcineurin inhibitor levels, etc) and confirmed three days following the first sample, it is recommend that an evaluation for BK viruria be initiated. Renal biopsy may be considered and if done, the tissue obtained should be processed to include immunohistochemistry/electron microscopy to evaluate for polyoma-associated nephropathy.

Subsequent management should be determined in accordance with standard practice after consultation with appropriate specialists (Nephrology and/or Infectious Diseases, based on biopsy results). International published recommendations for the diagnosis and management of BK-associated nephropathy[4] may be a useful guide for subsequent subject management.

7.4 Repeating Fasting Plasma Glucose to Determine Insulin Independence

Endpoint visits are scheduled at Day 75, 365 and one year post-transplant. At the visits on these days, the central lab sample for fasting serum glucose and c-peptide/creatinine should be drawn and sent for analysis at the University of Washington, as noted in the CIT-06 SOE.

If the result from the first sample is >126 mg/dL, the test should be repeated as soon as possible after the results are received from the University of Washington. If the result of the second sample is ≤126 mg/dL, the test should be repeated again (a third time).

Because repeat testing may be required to determine insulin independence at endpoint visits, coordinators may draw all three fasting glucose samples and freeze the two extra (or repeat) samples at these visits. If this approach is taken, the three samples must be drawn on three different days. Tubes from bulk supply should be used to collect the repeat samples.

7.5 Archived Serum Samples and Genetic Testing

As part of the informed consent process, subjects can decline to have samples stored and used for future genetic testing. If a subject declines to have blood samples collected and stored for future research studies, the sites *should not collect* the Serum to archive, Plasma to archive, or DNA to archive samples. If a subject declines to have blood samples collected and stored for future genetic (*i.e.* DNA) testing, then the DNA sample should not be drawn.

8 Instructions for Other CIT Procedures

8.1 Determining Insulin Independence

The definition of insulin independence in the CIT-06 study has five parts:

Islet transplant recipients will be considered insulin-independent with full islet graft function if they are able to titrate off insulin therapy for at least 1 week and all of the following criteria are met:

- One HbA1c level, one fasting serum glucose level, and a Mixed Meal Tolerance Test are documented within the visit window (e.g. 70-80 days at Day 75) and 7 consecutive days of blood sugar and insulin readings are documented within +/- 7 days of the visit window (e.g. 63-87 days at Day 75;
- HbA1c $\leq$ 6.5% or a $\geq$ 2.5% decrease from baseline (within 91 days prior to transplant);
- Fasting capillary glucose level should not exceed 140 mg/dL (7.8 mmol/L) more than three times in 7 consecutive days (fasting is defined as 1st blood sugar reading of the day not noted as post-prandial or bedtime;
- Post-prandial serum glucose $\leq$ 180 mg/dL (10.0 mmol/L) at 90 minutes during the MMTT;
- Fasting serum glucose level $\leq$ 126 mg/dL (7.0 mmol/L); if the fasting serum glucose level is > 126 mg/dL (7.0 mmol/L), it must be confirmed in an additional one out of two measurements;
- At least one MMTT fasting or stimulated c-peptide $\geq$ 0.5 ng/mL.

Insulin independence is the secondary endpoint in the CIT-06 study, and therefore it is important that complete data be collected to allow determination of insulin independence for all subjects.

Regarding the capillary blood glucose levels described in the insulin independence definition, in order to determine insulin independence, it is essential for subjects to record meal codes on their Blood Sugar Record Source Documents for the 7 days prior to their clinic visits (especially the Day 75 visits).

In these 7 days, to ensure that there is sufficient data present to determine insulin independence, the subjects must record at least:

- 7 fasting blood glucose readings
- 21 2-hour post-prandial blood glucose readings

The c-peptide values necessary to evaluate insulin independence must be obtained from central lab results (from the University of Washington).

To indicate that a subject is not using insulin, it is necessary to enter daily insulin usage as 0 units when completing a subject's Blood Sugar Record and HYPO eCRF. Leaving insulin usage blank will not be reflected as 0 units of insulin in the endpoint analysis.

8.2 Hypoglycemia and Insulin Use Top Eleven

- Meal codes are required for the 7 days prior to a clinic visit (particularly important at Day 75).
- If the subject required assistance to treat hypoglycemia, it is a Grade 3 adverse event AND a hypoglycemic event—HYPO log needs to be filled out. It may or may not be a SERIOUS adverse event.
- Subjects are not required to fill out complete blood sugar records during year 2 of follow-up, but all hypoglycemic events must be reported (HYPO log filled out, possible SAE).
- Insulin usage is required at the Y2 visit—for 7 days within the 90-day window around the Y2 visit.
- From the time of enrollment, all blood sugars <54 mg/dL (3.0 mL/L) must be reported on the Blood Sugar Record and Hypoglycemic Events eCRF. If the subject required assistance, the events also need to be reported as Grade 3 adverse events.
- Pre-transplant, only the hypoglycemic events that meet criteria for seriousness (hospitalization, PI opinion, risk of permanent impairment, etc.—also corresponds to Grade 4 in the TCAE--unconsciousness) should be entered on the Adverse Event eCRF.
- Post-transplant, all hypoglycemic events Grade 3 (required assistance) and above should be reported on the Adverse Event eCRF—and serious hypoglycemic events (hospitalization, PI opinion, risk of permanent impairment, etc.) should be reported as serious adverse events.
- Data entry is required for 28 days surrounding the visits marked with an X in the "Blood Sugar eCRFs" row of the SOE.
- 28 days with 4 readings each required to calculate the HYPO score—the 28 days must be within 35 consecutive days.
- 2 consecutive days with 7 readings each are required to calculate the LI.
- Do not report hypoglycemia that occurs during study-related procedures (such as FSIGT and MMT) as a HYPO event (on the Blood Sugar Record eCRF) or as an adverse event (on the Adverse Event eCRF). However, please do make a note documenting the event in the comments section of the specimen tracking system when you scan the samples that were drawn during the procedure that precipitated the event.

8.3 Crossmatch

Banked serum (up to 30 days old) may be used for crossmatch testing as long as the subject has not experienced an infection or had a transfusion of blood products during that 30-day period. If banked serum is used for crossmatch testing, the testing need not be repeated upon admission unless the subject has experienced an infection or blood products transfusion.

Virtual crossmatch results are not sufficient documentation of crossmatch negativity for the CIT studies.

8.4 Atherogenic Profile

If there is no hypertriglyceridemia (>400 mg/dL), the LDL will be calculated, if there is hypertriglyceridemia then the LDL will be measured directly.

8.5 Timing of Islet Infusion

The islet transplant must be started within 6 hours of completion of manufacture (i.e., filling the islet bag[s]). Any departure from this specification should be reported as a major protocol deviation, and the site should notify the NIH Medical Monitor and Senior Regulatory Officer immediately.

8.6 Etanercept Dosing

The CIT-06 protocol specifies a dose of 50 mg IV on Day 0 (1 hour prior to transplant) and 25 mg SC on days 3, 7 and 10 post-transplant.

The Day 0 dose should be diluted in 100 mL normal saline and infused IV in the operating room over 30 minutes. The infusion should be completed before the islet infusion is initiated.

8.7 ATG Administration

The three pre-transplant infusions of ATG for the initial transplant are suggested to be administered according to the following algorithm.

Table 2: ATG Administration Algorithm for Initial Transplant

Time	Sample Day	Sample Time	Activity
0 hour	Day -2	1600	Viable islet prep into culture
0-12 hours	Day -2/Day-1	1600-0400	ATG #1 over 6-12 hours
12-18 hours	Day -1	0400-1000	Rest over 6 hours
18-24 hours	Day -1	1000-1600	ATG #2 over 6 hours
24-32 hours	Day -1	1600-2400	Rest over 8 hours
32-38 hours	Day 0	2400-0600	ATG #3 over 6 hours
38-44 hours	Day 0	0600-1200	Preparations for Transplant
44 hours	Day 0	1200	Islet Transplant

In cases in which the initial islet transplant does not occur, the subject should remain on the maintenance immunosuppression required for the kidney. When another pancreas becomes available, investigators should use clinical judgment to determine the appropriate induction regimen for the subject. The following guidelines can be used in this determination:

- < 12 weeks after failed transplant, if subject has received only first 2 doses (day -2 and day -1), then give 3 doses of 1.5 mg/kg on days -2, -1, and 0.
- If subject has received all 3 doses (day -2, day -1, and day 0) with failed transplant, investigator should determine whether to give 2 doses of 1.5 on day -2 and -1 or 3 doses of 1 mg/kg on days -2, -1, and 0.
- If a pancreas becomes available more than 3 months after initial ATG administration, administer all doses as outlined in protocol section 5.2.1.1

These guidelines are based on the assumption that most subjects will have received 2 doses of ATG (1.5 mg/kg total) at the time of the initial (failed) islet transplant. The dose should be

limited as described in the CIT06 protocol Section 5.2.1.1 in patients treated with depleting antibody induction therapy for their renal transplant within the last year. Specifically, the same ATG protocol will be followed as with a patient who has not received a T cell depleting therapy within the last year except that the doses on day +1 and day +2 will be omitted. The patient will thus receive a day -2 dose of 0.5 mg/kg, a day -1 dose of 1.0 mg/kg and a day 0 dose of 1.5 mg/kg resulting in a total dose of 3 mg/kg instead of 6 mg/kg.

8.8 Heparin Administration

The CIT protocols describe the administration procedures for heparin. It should be noted that the 70 U/kg body weight of recipient dose should be equally divided among the islet bags, and then given with the islet transplant. In addition, the heparin given in the 48 hours post-transplant should be administered intravenously.

8.9 Islet Administration and Portal Pressure Guidelines

The CIT protocols contain study-mandated requirements for islet administration and portal pressure measurements. Additional guidelines for islet administration and portal pressure measurements are provided below; however, each participating site should follow its site-specific standards to ensure compliance with institutional guidelines and subject safety.

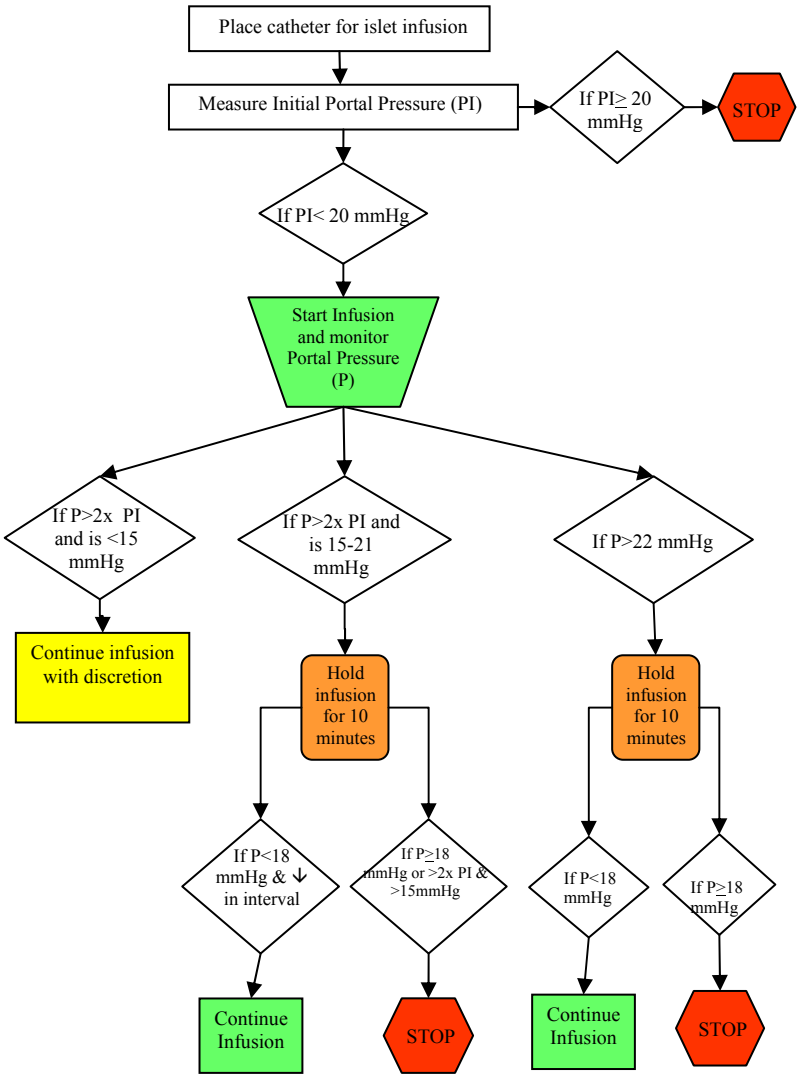
8.9.1 Islet Administration Guidelines

For percutaneous access, a local anesthetic agent (lidocaine) is injected subcutaneously, and a fine Chiba needle is used to puncture a peripheral branch of the portal vein. Tiny amounts of angiographic contrast media are used to confirm satisfactory location of the puncture site in a peripheral portal vein. A thin, flexible guide wire is threaded into the main portal vein and the Chiba needle is exchanged for a 3 to 6 French catheter (*e.g.*, O'Kelly islet catheter, 6-Fr Accustick stiffened micropuncture introducer set, Cook Inc.). This catheter is threaded over the guide wire to position the tip in the main portal vein. A contrast portogram will be obtained using minimal contrast exposure, and the portal pressure is monitored by hooking up to an in-line pressure monitor via a 3-way tap, after zeroing the monitor to room air pressure. Elevated absolute intraportal pressures (>20 mmHg/ 27 cm H_2O) confirmed at the beginning of the procedure is considered a contraindication for continuing with the transplant infusion.

For laparotomy, under general anesthesia, a small incision is made in the abdominal wall, the peritoneal cavity is entered and a short segment of small bowel or omentum exposed. A satisfactory mesenteric or omental vein is cannulated with an angiocath or angiographic catheter. This may or may not be advanced into the portal vein and venogram performed. The islet mixture can then be infused.

8.9.2 Guidelines for Portal Pressure Monitoring and Maintenance During Islet Infusion

Figure 4: Portal pressure algorithm monitoring during islet infusion



If the intraportal pressure rises above 22 mmHg (30 cm H2O), the infusion should be held for 10 minutes; if after that time the portal pressure falls below 18 mmHg (25 cm H_2O) the infusion may continue, if not, the infusion should be terminated.
If there is a change in absolute portal pressure that exceeds more than double the baseline recording and the reading is between 15-21 mmHg (20.4 – 28.5 cm H_2O), the infusion should be held for 10 minutes. If after that time the portal pressure demonstrates an interval reduction and is less than 18 mmHg (25 cm H_2O), the infusion can continue. If, however, the pressure remains greater than 18 mmHg (25 cm H_2O) or is more than 15 mmHg (20.4 cm H_2O) and greater than twice the opening pressure, the infusion should be terminated.
If there is a change in absolute portal pressure that exceeds more than double the baseline recording and the reading is less than 15 mmHg (20.4 cm H_2O), the infusion may be continued at the discretion of the physician attending the infusion.

Subsequent sub-lots should only be administered if the portal pressure remains below 18 mmHg (25 cm H_2O) and less than twice the opening portal pressure.

For percutaneous transhepatic procedures, the catheter tract is embolized through its entire length as the catheter is removed completely, and the subject returns to the ward with instructions to lay recumbent on the right side for 4-6 hours as tolerated.

It is recommended that vital signs are monitored every 15 minutes for the first hour, every 30 minutes for one hour and hourly up to 6 hours. Once the recovery from the procedure is complete

and there is no clinical suspicion of acute complication, vital signs are monitored every shift or every 8 hours.

8.10 Tuberculosis (TB) Testing

Investigators may select from the two methods of TB testing: the traditional tuberculin skin test (TST) or the new QuantiFERON®-TB Gold test (QFT) ®[1]. The CDC recommends that the QFT can be used in all situations in which the TST is normally used.

Both the QFT and the TST are known to give indeterminate results in some situations. If an indeterminate result is encountered, investigators should use their institution's protocol for following up on an indeterminate TB test result. Any subject who has been treated for TB, or who plans to receive treatment for TB, is not eligible for the protocol. If it is unclear whether a subject is eligible under this criterion, please contact one of the DCC Protocol Coordinators.

8.11 Definition of Severe Hypoglycemic Events

In the CIT studies, a severe hypoglycemic event is defined as: an event with one of the following symptoms: memory loss; confusion; uncontrollable behavior; irrational behavior; unusual difficulty in awakening; suspected seizure; seizure; loss of consciousness; or visual symptoms, in which the subject was unable to treat him/herself and which was associated with either a blood glucose level < 54 mg/dL [3.0 mmol/L] or prompt recovery after oral carbohydrate, IV glucose, or glucagon administration).

According to this definition, the subject must be unable to treat him/herself. For the purposes of the CIT studies, "unable to treat" means that the subject was physically incapable of procuring whatever was needed to treat his/her hypoglycemia (for example, s/he was too weak or dizzy to get a glass of juice or glucose tablets). A subject who is alerted to his/her hypoglycemia by a friend, family member or hypoglycemia-sensing dog is experiencing a severe hypoglycemic event only if s/he is physically incapable of acquiring the means to treat him/herself.

8.12 CIT-06 Screening Log

A CIT-06 Screening Log is provided in Appendix 13. It is a tool that allows the study coordinator to collect data on potential subjects who screened out of the CIT-06 study due to certain inclusion/exclusion criteria. The DCC will request that sites submit the data collected on a quarterly basis. Site coordinators can collect the data on any screening log of their choosing, but the data must be submitted to the DCC on the log in Appendix 13. No subject identifiers should be included on the screening log; it is only to be used for tallying potential subjects lost and the values that excluded them from the CIT-06 study.

8.13 Checklist for Inclusion/Exclusion Criteria

A checklist to assist in subjects' eligibility based on CIT-06 inclusion/exclusion criteria is included in Appendix 14. Study coordinators are not required to complete or file a copy of this checklist. However, completing and filing the checklist with an investigator's signature at the bottom is a simple way to document that a subject meets all inclusion/exclusion criteria. Study monitors will seek additional source documentation of items in the checklist that are highlighted in grey. The investigator's signature on the checklist can serve to document that s/he has assessed the criteria that are not highlighted and believes that the subject meets the criteria.

8.14 Documentation of Non-Endocrinologist Diabetes Specialists

The CIT-06 inclusion criteria require subjects to have been seen by an endocrinologist, diabetologist or diabetes specialist 3 times in 12 months prior to enrollment in a CIT study. Subjects who do not meet this criteria must begin intensive insulin therapy after enrollment. Subjects who are seen by a "diabetes specialist" such as an internist, a physician's assistant, a nurse practitioner or other primary caregiver should have that person complete the questionnaire included in Appendix 3. At least the last three questions on the questionnaire must be answered "yes" in order for the doctor or other provider to qualify as a "diabetes specialist" for the purposes of the CIT studies.

The presence of this completed questionnaire in the subject's research file is required to document that the subject is involved in intensive insulin therapy as defined in the islet alone protocols. Subjects whose diabetes care is provided by a board-certified or qualified endocrinologist or diabetologist do not need to have this completed questionnaire in their research file.

8.15 Epstein-Barr Virus (EBV) IgG

According to the protocol, subjects will be excluded who test negative for EBV IgG at the time of screening for the study or their previous kidney transplant. If it is known that a subject previously tested negative at the time of the kidney transplant and later tests positive at the time of screening for the study, the subject will be excluded.

8.16 Carotid Intima-medial Thickness

The carotid ultrasound assessments will be conducted at time points specified in the SOE. Instructions and associated study instruments will be provided separately from this CIT-06 Manual of Operations, when available.

8.17 Blood Pressure

The blood pressure should be measured using a reliable automated blood pressure monitor **which is calibrated every six months**. The correct cuff size is determined by measuring the circumference of the arm midway between the elbow and shoulder. The cuff width should be equal to 80% of the circumference.

Blood Pressure Measurement

1) With participant seated, palpate the brachial artery. Wrap cuff with the center of the bladder over the brachial pulse. Ensure that the bottom edge of the cuff is about 3.5 - 4.0 cms (2 inches) above the antecubital fossa. Cuff should be loose enough to permit the insertion of two fingers between the cuff and the arm.

2) Elevate the arm to a level even with the heart. Have the participant rest quietly for five minutes before BP is measured. The legs should be uncrossed with feet flat on the floor. The participant should be instructed not to speak while their BP is being measured.

3) Monitor should always be positioned to face away so that readings cannot be seen by the participant.

4) Take three blood pressure readings at 1 minute intervals and record blood pressures, pulse and Mean Arterial Pressure (MAP). For analysis, only the second and third measurement will be used.

Management of Hypertension

1) If the blood pressure is >135 systolic, or >85 diastolic, schedule subject for a recheck in two weeks. If the BP remains elevated at that time schedule subject for another recheck in two weeks. If the BP at the third consecutive visit is elevated notify the subject and the study physician. The diagnosis of hypertension should be documented and the study physician should refer the subject to the appropriate practitioner who may prescribe anti-hypertensive therapy using their own choice of medications.

2) The blood pressures should be checked 1-2 weeks following the initiation of drug therapy and the medication should be titrated to achieve a goal of ≤130/80 mmHg. The blood pressures should be checked at 1-2 week intervals until the study goals are achieved.

8.18 Quality of Life (QOL) Questionnaires

The CIT studies require administration of four (4) QOL questionnaires: the SF-36 Health Survey (SF-36), European Quality of Life Index (EQ-5D or EuroQoL), Diabetes Distress Scale (DDS), and the Hypoglycemic Fear Survey (HFS). Please refer to the SOE in the protocol for details regarding the specific time-points when the subjects will complete the QOL questionnaires. The instructions below apply to all time-points indicated on the SOE, including the questionnaires completed while the subject is on the waiting list.

The QOL questionnaires must be completed by the individual subject. In order to assure confidentiality, the questionnaires are printed on two-part paper. The SC will label a set of questionnaires with the appropriate Subject ID number and the appropriate date, and then give the documents to the subject to complete. This process should occur in a place where the subject can be confident that he/she has privacy.

The QOL questionnaires must be scanned through the STS. QOL questionnaires must be scanned in the "Prepare for Visit" step, when the coordinator is assigning a kit to a study subject prior to his/her clinic visit. However, since the subject will seal the completed questionnaires into envelopes after completing them (see below), it is important to place a single extra barcode label (taped into the top of the kit box) on the white envelope. Use only one barcode label per set of four questionnaires. Do not attach any barcode labels to the questionnaires themselves, only the envelopes. Do not attach a label to the manila envelope.

In the WL/BL portion of the CIT06 study, QOLs are required every 3 months according to the SOE.

Once the subject has completed the questionnaires, the subject will be asked to:

1. Separate the two parts (white and yellow portions) of each questionnaire;

2. Place the original copy (white portion) into a designated white envelope that has been labeled with the appropriate Screening ID or Subject ID number;

3. Place the second copy (yellow portion) into a designated manilla envelope that has been labeled with the appropriate Screening ID or Subject ID number;

4. Seal both envelopes and return both to the SC.

The SC sends the white envelope via Federal Express to the DCC, where the data from the questionnaires will be entered into the database by the DCC data entry staff. The SC may batch a group of subjects' white envelopes and ship them on a monthly basis. The barcodes on the white envelopes must be scanned in the "Ship Specimens from Lab" section of the STS before the QOLs are shipped. The manila envelope will remain sealed and will be stored in the subject's research file, in case the originals are lost.

The site will use the CIT Consortium Federal Express account number to ship documents to the DCC: **Federal Express Account # 272997896, Reference number 500008533.**

University of Iowa, Department of Biostatistics
Clinical Trials Statistical & Data Management Center
CIT Lead Coordinator
201 S. Clinton St.
2400 UCC
Iowa City, Iowa 52240-4034
Phone: 319-353-3041
Email: isletstudy@uiowa.edu

8.19 Assessing Clinical Significance of Laboratory Tests

The study coordinator must review all laboratory reports to identify abnormal values.

- All abnormal values for labs listed in the *Terminology Criteria for Adverse Events (TCAE) in Trials of Adult Pancreatic Islet Transplantation* must be graded according to the islet TCAE and recorded as AEs in the DCC Database and in the Source Document, if required by the protocol.
- All abnormal values for labs **not** listed in the islet TCAE must be signed, dated and labeled as Clinically Significant (CS) or Not Clinically Significant (NCS) by the PI or designee (the designee must be a physician on the 1572). Abnormal lab values must also be graded in the Source Document. If the laboratory results are assessed as CS and meet the protocol's requirements for AE Reporting, they should be recorded as an AE in the DCC Database and in the Source Document.

The PI or designee is responsible for submitting any SAEs that are associated with abnormal lab values. All laboratory values listed as adverse events should be repeated until they return to normal or until the investigator determines that the subject's condition has become stable, and the investigator does not expect any further improvement or worsening.

There are two options:

- The event is considered ***Resolved*** if the subject returns to his/her pre-event status, or better; OR

- The event is considered ***Resolved with sequelae*** if the subject has stabilized and a new, more severe level of chronic abnormality persists for three months or more.

Versioning of the TCAE does not coincide with versioning of the protocol and other study materials. Always use the most current version of the TCAE, which can be found at the CIT website, www.isletstudy.org.

8.20 Glucometer Quality Control (QC)

Subjects will record their blood sugar levels on the Blood Sugar Record source document using a glucometer, the One Touch Ultra Meter made by LifeScan. In order to verify consistent and accurate results from the glucometer, routine QC should be implemented both by the subject and the site SC.

8.20.1 Subject QC

The site SC should instruct the subject to follow the QC instructions outlined in the glucometer package insert. Provide the subject with the following reminders upon receipt of the glucometer:

1. Enter the code present in the test strips into the glucometer prior to testing.
2. Before using the meter for the first time, practice the procedure using control solution. Mark the test as a control solution test to ensure the result does not get stored in the meter memory as a blood glucose results. When three tests in a row show results within the expected range, you are ready to test with blood.
3. Thereafter, perform a control solution test in the following situations:
   - when opening a new vial of test strips
   - once a week
   - when there is suspicion that the meter or strips are not working properly
   - when blood glucose measurements are not consistent with how the subject feels
   - if the meter falls

   Possible explanations for test results of control solution outside the expected range include:

   - An error in performing the test
   - failure to shake the control solution before use
   - expired or contaminated control solution
   - improper coding of the meter
   - test strip deterioration
   - meter malfunction
   - control solution that is too warm or too cool
   - failure to discard the first drop of the control solution

Instruct subjects to contact the site SC if they continue to receive test results outside the expected range.

8.20.2 Study Coordinator QC

The site SC should perform a control solution test on the subject's glucometer at each study visit. Additionally, a comparison test should be performed each time central metabolic labs are being drawn (*i.e.*, fasting serum glucose, MMTT, and FSIGT). Instruct the study subject to perform a capillary finger stick using the glucometer within 30 minutes of the first blood draw for glucose. When the site receives the glucose result from the central lab, it should be compared with the result of the capillary finger stick. If the variability is less than 15% compared to the central lab result, and the meter passes the test with the control solution, then the meter results can be assumed to be accurate. If the variability is determined to be 15% or greater, as compared with the central lab result, the site coordinator will follow-up with the subject and decide whether to replace the meter.

8.20.3 Downloading Glucometer Information

The software for the One Touch glucometer will be provided to each center. The software is very user-friendly. When you open the software for One Touch you will be able to *Download Meter Readings, View Reports, Manually Enter Data, or Setup.*

Click on *Download Meter Readings* then follow the steps.

Step 1 – Attach the meter to your computer using the USB cable.

Step 2 –If your meter is blue, turn it OFF before downloading, if the meter is gray, turn if ON before downloading.

Step 3 – Click on *download*. Follow the prompts for adding a new subject's name and data. You can change the reports and date range as needed. You will use this information to verify the information the subjects have provided on the Blood Sugar Record and Hypoglycemic Sheet source documents.

8.20.4 Use of LifeScan Ultra Glucometers

Lifescan Ultra2 glucometers are available to subjects through a Clinical Trials Agreement between NIH and Lifescan. It is recommended that subjects use the Lifescan Ultra2 glucometers that are provided by CIT. However, a subject who already uses a Lifescan glucometer in the Ultra family of meters (Ultra, Ultra2, UltraSmart, UltraMini or UltraLink) may continue to use this glucometer to collect blood glucose data for the CIT blood sugar record source documents.

Blood sugar records that are collected for evaluating inclusion/exclusion in a CIT islet-alone study or for calculating the MAGE (7 days prior to each visit that includes metabolic assessments) must be verified with data collected on a CIT-issued or on a subject's personal Lifescan Ultra glucometer. At each study visit, the study coordinator should check with the subject to ascertain whether his/her glucometer is in good working order and whether the subject needs a new supply of strips for the glucometer.

If a subject who is using a CIT-issued glucometer loses the meter or it malfunctions, the subject should notify the clinical site as soon as possible. The site should issue the subject a new CIT glucometer immediately, sending it by Federal Express if necessary. Until the

subject receives a new CIT glucometer, s/he should use his/her own glucometer to continue collecting blood sugar data. As soon as the subject receives the new CIT glucometer, s/he should begin using it to collect blood sugar data and discontinue using his/her personal glucometer.

8.21 Continuous Glucose Monitoring System® (CGMS)

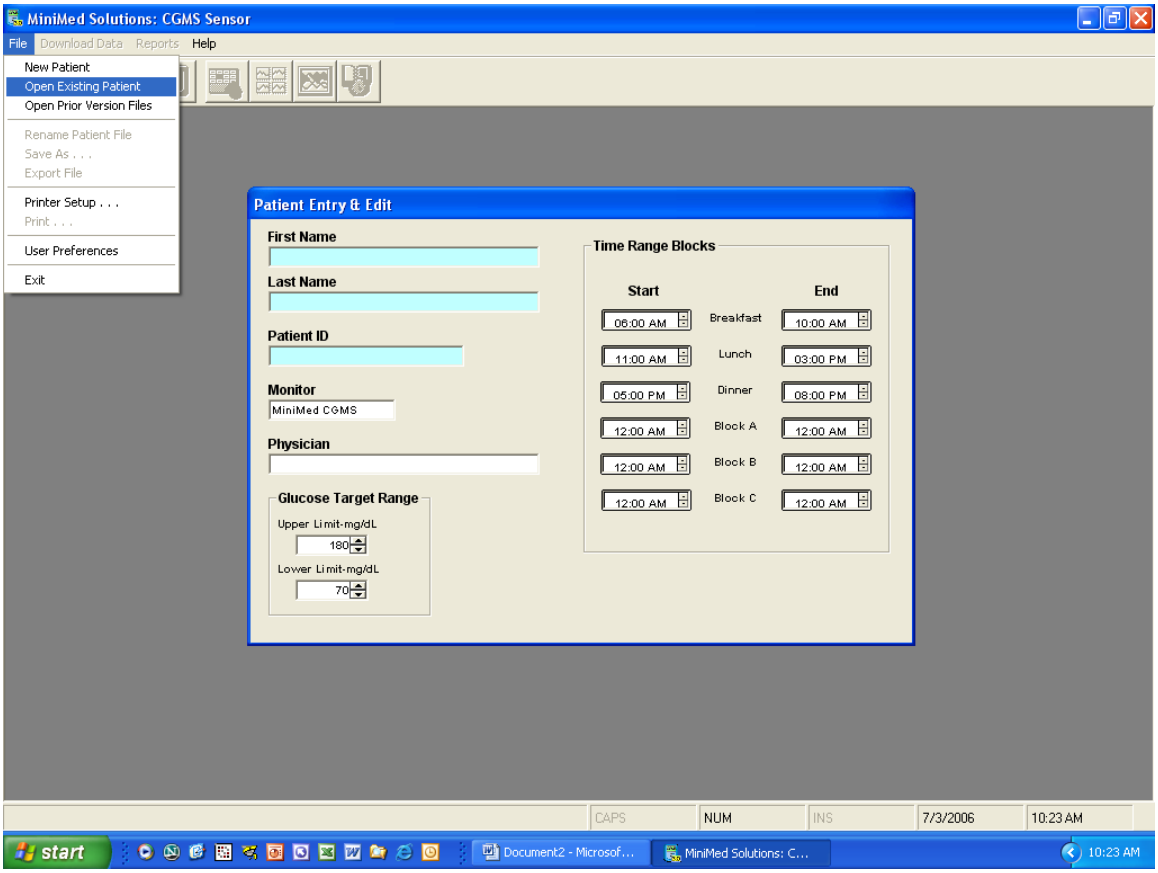
CIT provides clinical sites with CGMS Gold or IPro monitors for use in the CIT studies. These units should be used to collect the data for the 72-hour periods described in the protocol SOEs. However, if a subject is already using a different CGMS within the Medtronic family (Gold, IPro or Paradigm), it is acceptable for study coordinators to download the data from the subject's own CGMS and submit it to the DCC as described below.

The CGMS® system collects data in files that can be downloaded and saved on the user's personal computer. These files are fixed format and cannot be changed by the user. A coordinator or investigator at the site will download this file from the CGMS® device onto a personal computer. The standard file name is made up of the subject's last name, first name initial, Screening or Subject ID, and the date. The file is saved with the "mmg" file extension. The following section instructs the site SC on how to rename the CGMS® .mmg files, removing subject identifiers, before transferring them to the DCC.

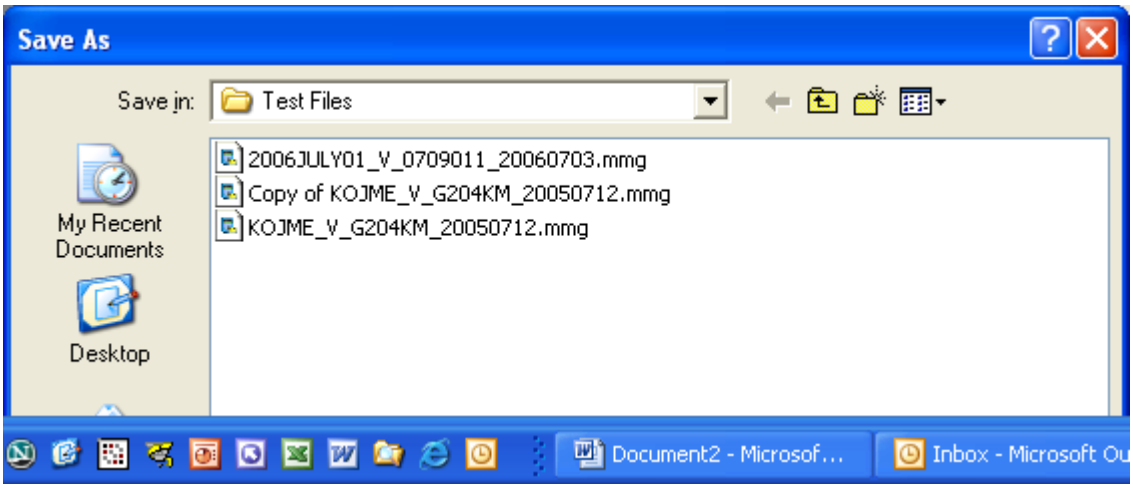
8.21.1 Renaming and Transferring .mmg Files to the DCC

When you are ready to send a data file to the DCC, you must remove all subject identifiers from the data except the Screening or Subject ID number, the visit number for which the data was obtained, and the date that the data was obtained. The CGMS® software provides a method for renaming a data file that will allow the user to provide this identifying data in the name of the file that is being provided to the DCC.

When the software is opened, the following screen appears.

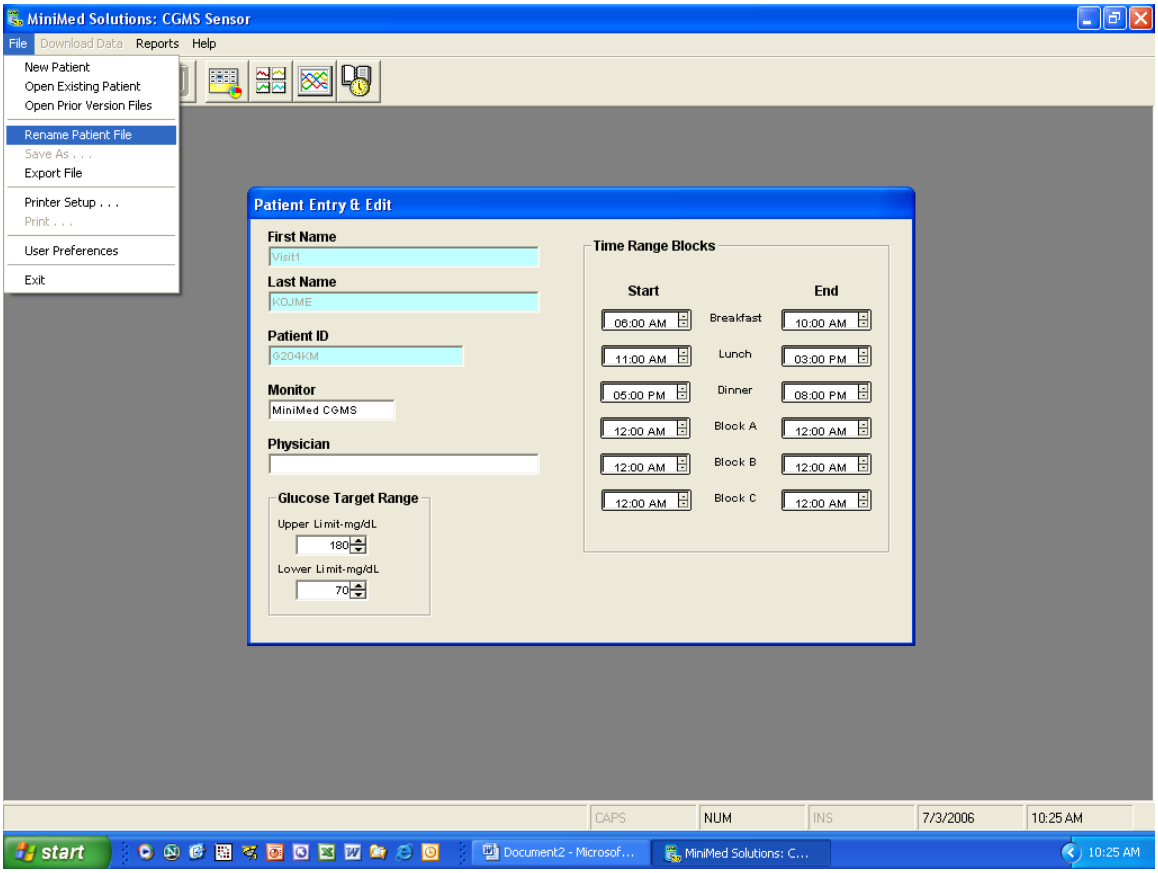


The user should select the "open existing file" option from the file menu and select the file to be sent to the DCC.

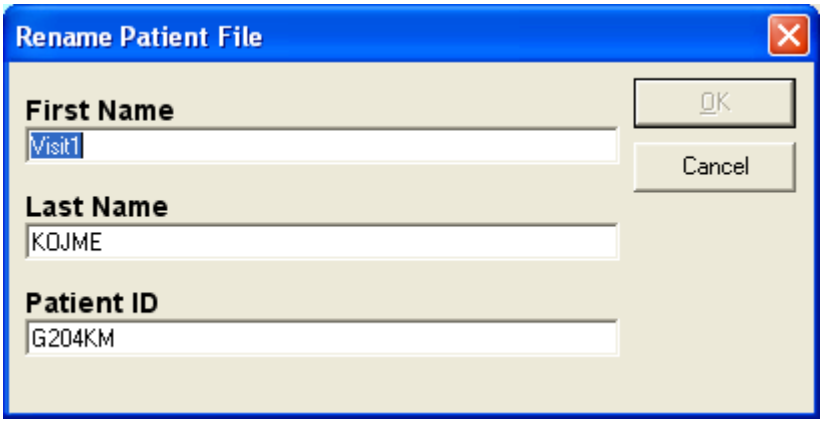


Files with the "mmg" extension will be sent. There are three listed here. The user will be required to navigate to the correct folder on his/her computer to find these files. The location of the folder depends on how the software was installed.

When the user opens the file, s/he will see the following screen. On the file menu, select the "rename subject file" option.

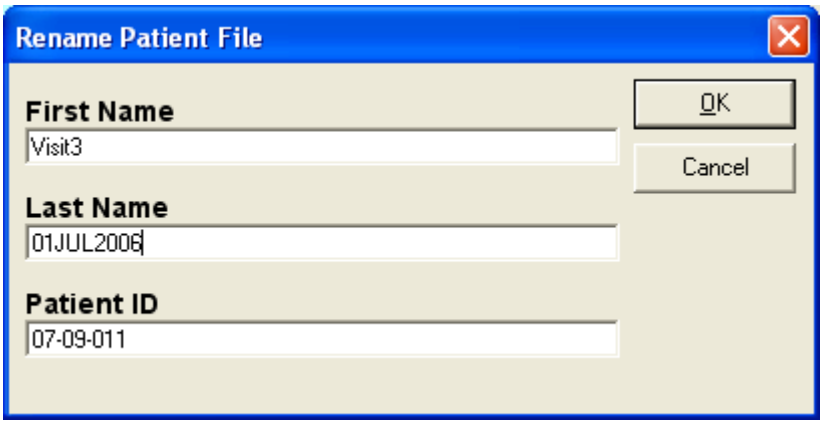


The user will then see the following window that reflects the name and ID used to create the subject. This information can be anything you want it to be. The user must change the values for the three fields before sending the file to the DCC.



In order for the DCC to be able to identify the data, the user must provide the visit number, the date that the CGMS® data collection period began and the subject's Screening or Subject ID number using the three fields on this window. Please do this carefully as it very important that the DCC have valid identifying information. The software uses the last name, first letter of the First Name, and Subject ID and the date the file was renamed to build a new file name (you will not lose the old file). Please enter the Visit Number from the SOE in the "First

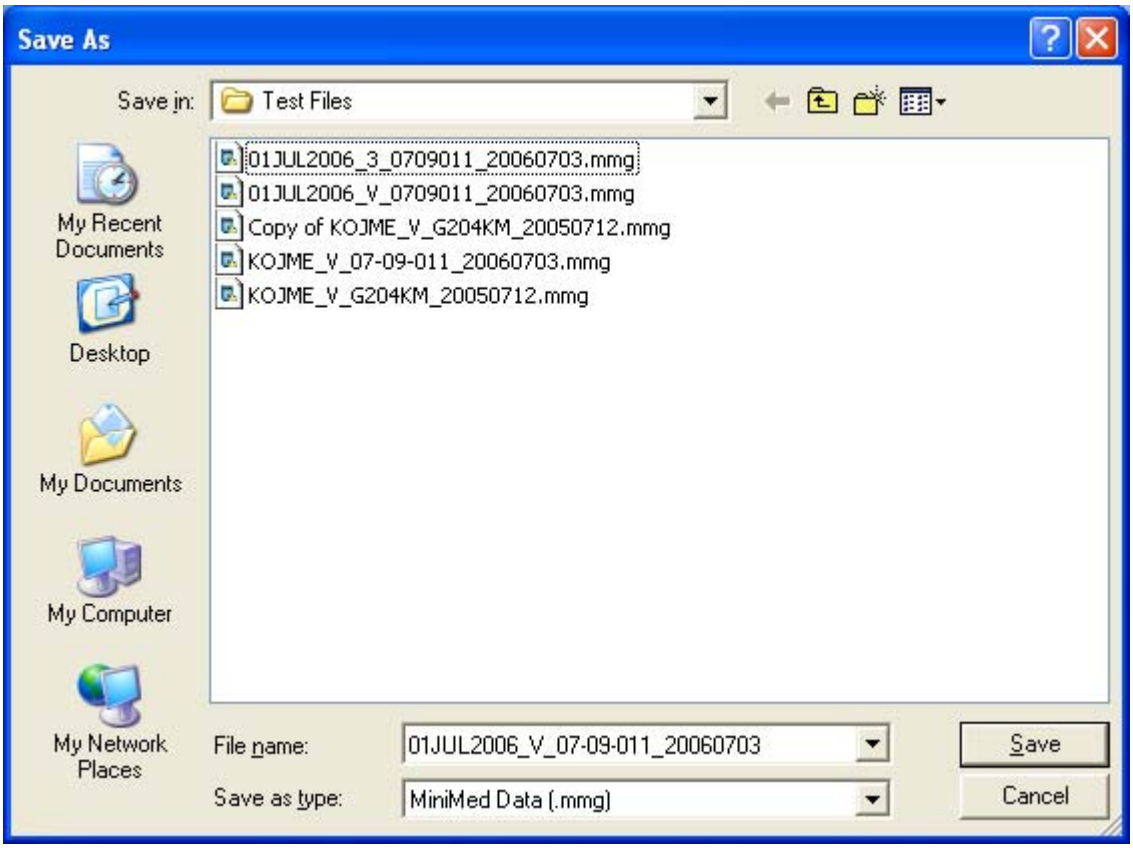
Name" Field, the date the CGMS® sample period began in the "Last Name" field, and the subject's Screening or Subject ID in the Subject ID field.



The CGMS® software creates a new file with the name

01JUL2006_V_07-09-011_20060703.mmg.

The software creates this file name from the information that you provided in the previous window. In this case, the 01JUL2006 was provided in the Last Name field, _V_ is there because you entered Visit3 in the First Name field, and 07-09-011 is the study assigned Subject ID number. This file was created on the third of July 2006.



Although the visit number does not appear in the file name, it is recorded in the data file (only a V appears in the file name). Select "Save" to complete the renaming function. A copy of

the original file with the new identifying information will be saved with the "mmg" extension. The original file will not be lost. Additionally, the original file should be maintained at the site in case something goes wrong with the data transfer.

The user should send an email with the renamed (new) file as an attachment to the following email address: CITData@uiowa.edu. Please include the following in your email:

- Your name
- The subject's Screening or Subject ID
- The study visit date from the SOE
- The date that the CGMS® collection period began.

The data center will store the file attached to the email and export it to a format that can be loaded directly into the CIT database.

8.22 Subsequent Transplants

Specific criteria and timing for subsequent islet infusions is detailed in the protocols. Do not complete the *Second Transplant Qualification* eCRF or the *Third Transplant Qualification* eCRF until a compatible islet preparation becomes available. This is similar to completing the *Transplant Eligibility* eCRF; it confirms, using the most recent results available, that the subject is eligible to receive a second or third islet infusion.

8.22.1 Timing of Subsequent Transplants

All subsequent transplants must be performed within 8 calendar months of a subject's initial transplant. For example, if a subject receives an initial transplant on January 1, 2010 and requires a second and/or a third transplant, both must occur before September 1, 2010.

8.22.2 Second Transplant

All protocols indicate that in order to be considered for a subsequent transplant, subjects must not meet criteria for insulin independence. Subjects with partial graft function or graft failure (including primary non-function) are eligible for a second protocol transplant. Subjects with graft failure (including primary non-function) are not eligible for a third transplant.

- If the subject has **partial graft function**, then s/he can receive a second transplant after *30 days* post first islet infusion if s/he meets the additional eligibility criteria outlined in the protocol. A site should ensure that these criteria are met and documented in the chart. Please refer to *Figure 5*. A source tool for documenting eligibility for a second transplant is included in Appendix 17.

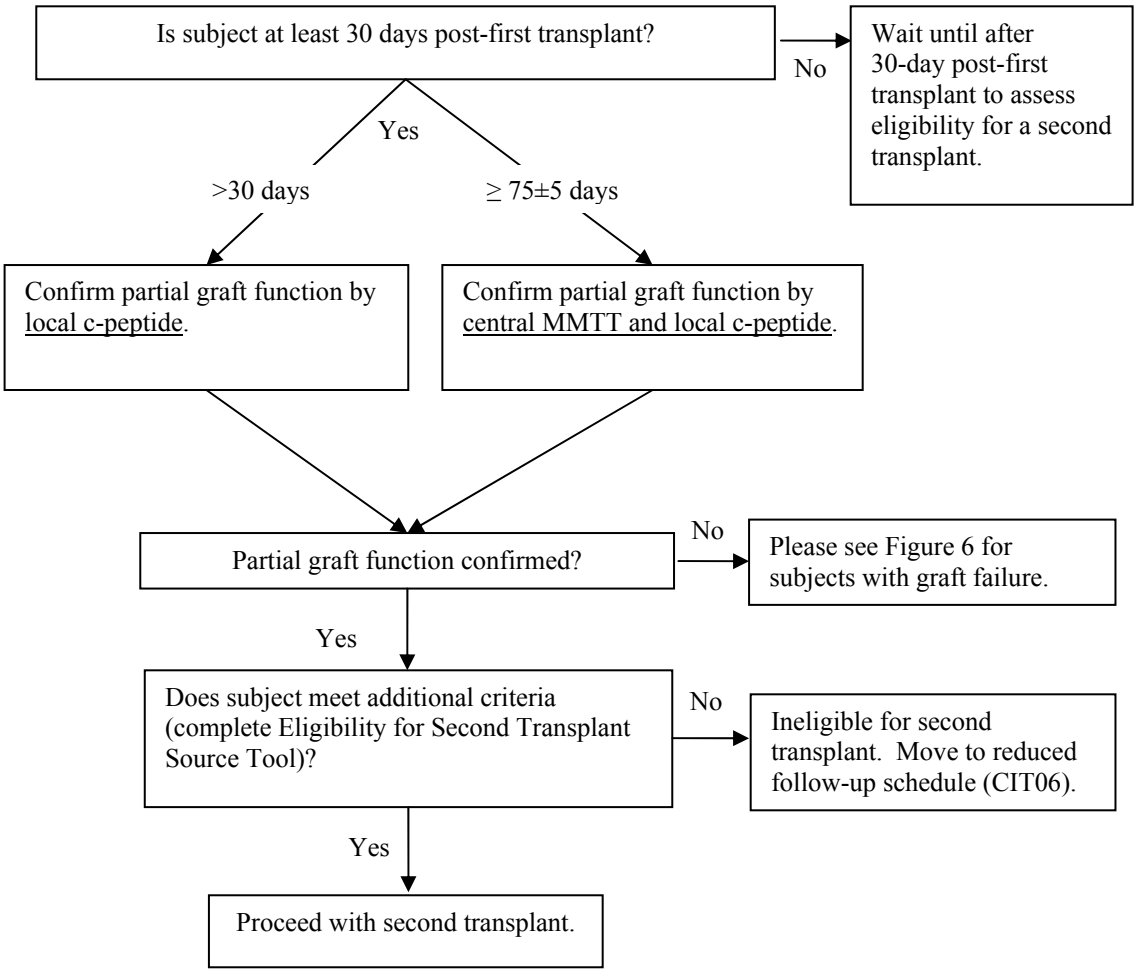


Figure 5: Second Transplant Qualification: Subjects with Partial Graft Function

- Subjects with **graft failure** can receive a second transplant with CIT Steering Committee (SC) approval. These subjects are not required to wait for day 30 post first islet infusion to become eligible for their second transplant. Once graft failure has occurred, the site should submit the following to the DCC: Please refer to Figure 6. A source tool for documenting eligibility for a second transplant is included in Appendix 17.

    - Results of graft failure assessments
    - Post-transplant clinical data
    - Potency testing from 1st transplant product
    - Additional assessments as needed

    The DCC will circulate the data to the SC for review. The site can move forward with the second transplant once written confirmation of the Steering Committee's decision has been received.

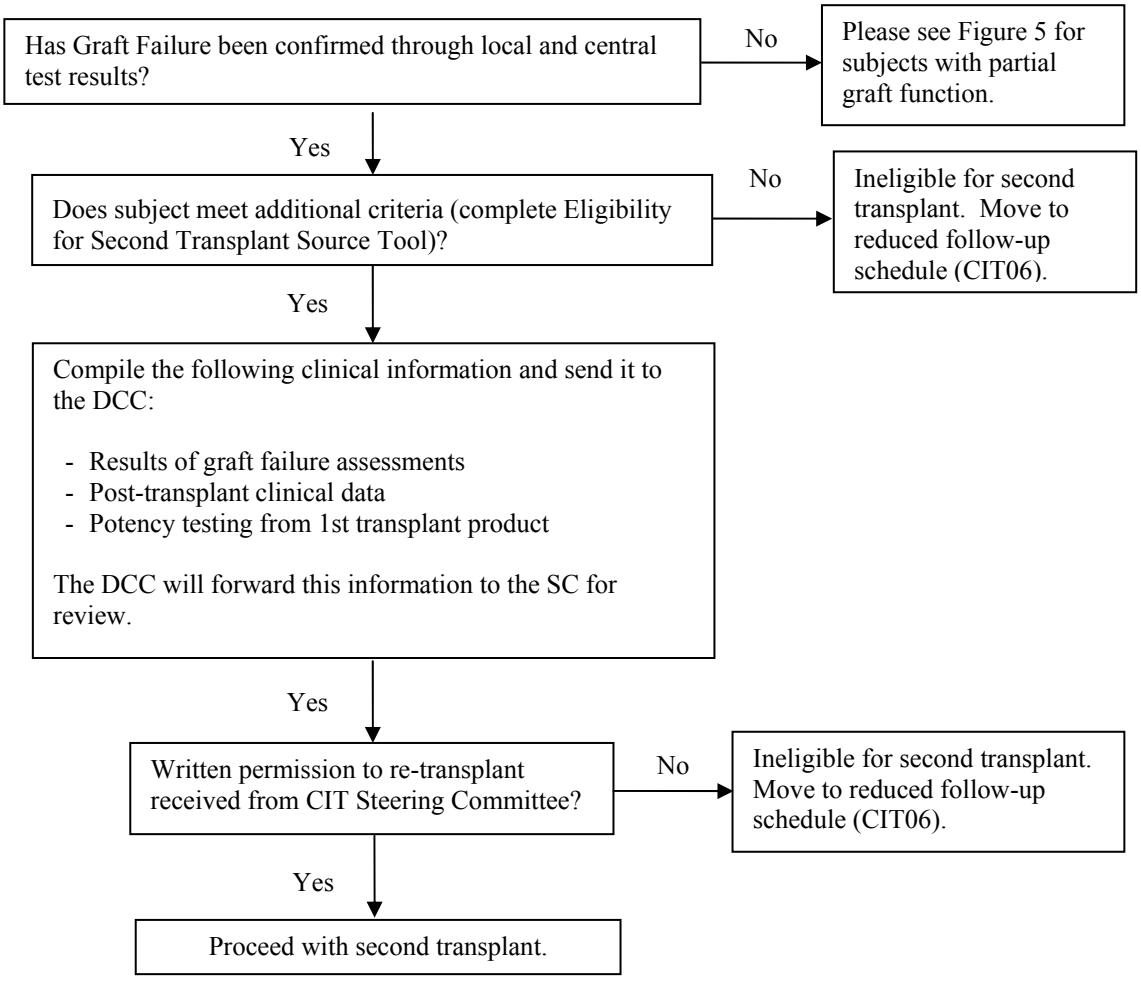


Figure 6: Second Transplant Qualification: Subjects with Graft Failure

8.23 Third Transplant

Subjects with graft failure (including primary non-function) are not eligible for a third transplant. Only subjects with partial graft function are eligible for a third transplant. CIT Steering Committee approval must be obtained before a third transplant is undertaken, and written confirmation of this approval from the DCC must be included in the subject's source documentation. Please refer to Figure 7. A source tool for documenting eligibility for a third transplant is included in Appendix 18.

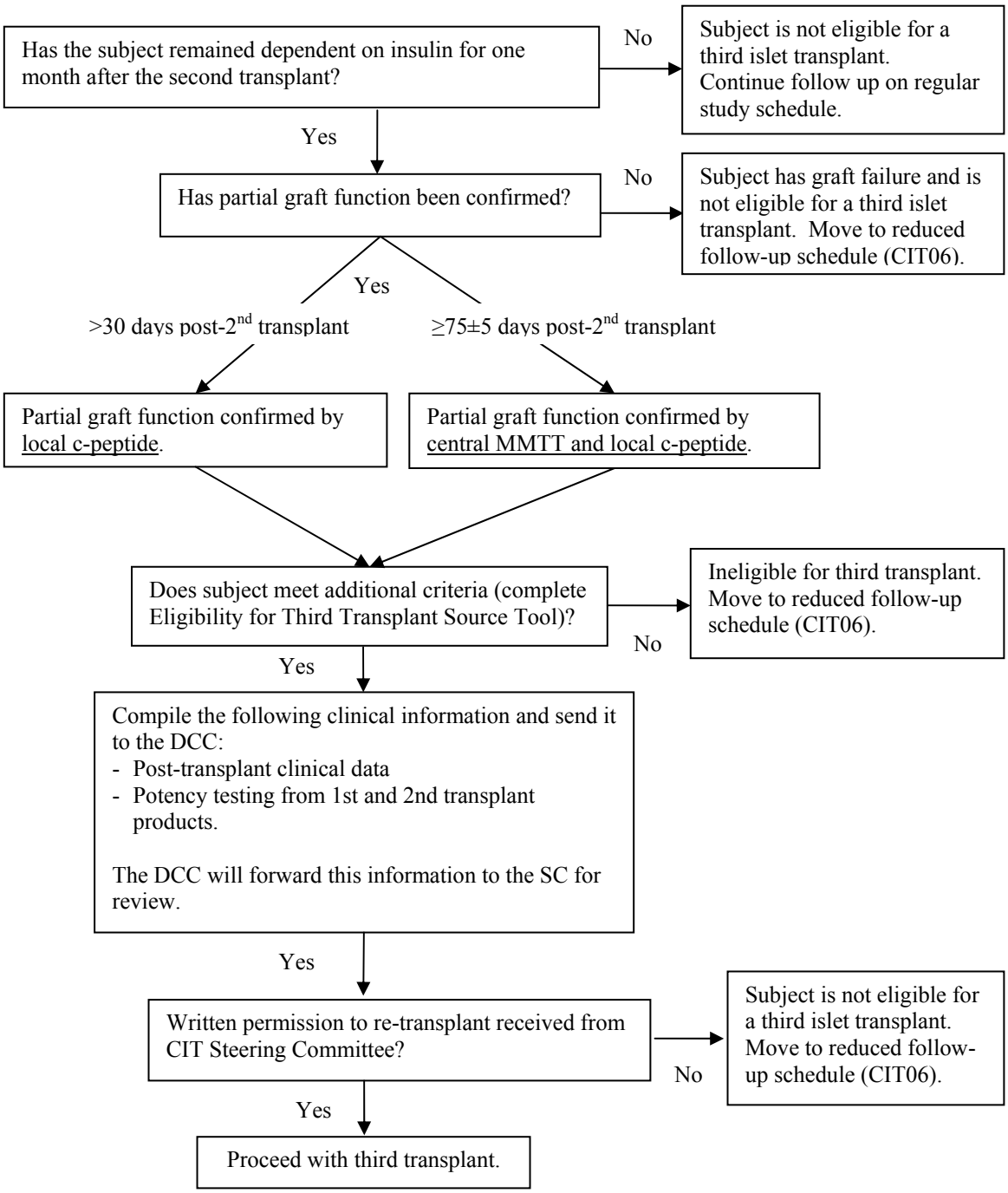


Figure 7: Third Transplant Qualification

8.24 End of Study Assessments

Some assessments are required at both Month 12 post-final transplant (M12) and Year 1 post-initial transplant (Y1) on the schedule of events. If a subject receives only one islet transplant as part of his/her participation in CIT, M12 and Y1 will occur on the same day. When this is the case, all of the assessments listed in both columns must be performed within the window listed for the Y1 visit, but the assessments listed in both columns do not need to be performed twice. In a similar fashion, the M24 and Y2 visits, and M36 and Y3 visits, can be combined for subjects who have received only one islet transplant; again, assessments listed in both columns do not need to be performed twice. Additionally, data does not need to be entered twice, e.g. once under M12 and again under Y1. Data only needs to be entered one time under the post-final transplant visit.

Following a second or third transplant, it is possible that the Day 75 visit for the subsequent transplant and the Y1 visit post-first transplant could coincide within a few weeks. If a subject in this situation is not willing or able to return to the clinical center for both the Day 75 and the Y1 visits, the Y1 visit containing the primary endpoint assessments should be prioritized.

8.25 Timing/Scheduling of Metabolic Assessments

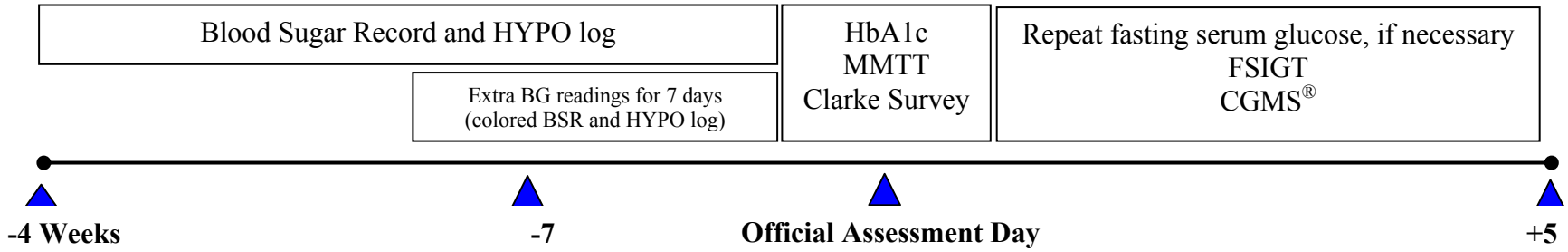


Figure 6: Timeline for metabolic assessments

Scheduling Instructions for Endpoint and Metabolic Assessments:

1. Schedule the official assessment day within the protocol-specified visit window.
2. Complete the HbA1c, MMTT, and Clarke Survey (for time points indicated on the SOE) on the official assessment day.
3. Collect the Blood Sugar Record and HYPO log from the subject for the 4-weeks prior to the official assessment day (including more intensive recordings collected on the colored source document for the 7 days prior to the official assessment day)..
4. For endpoint visits, if the subject meets other criteria for insulin independence, as defined in the protocol, repeat the fasting serum glucose if the result is > 126 mg/dL (7 mmol). Perform a 2nd repeat if the 1st repeat result is ≤ 126 mg/dL.
5. Complete the FSIGT within the visit window for time points indicated on the SOE.
6. Start the CGMS® within the visit window for time points indicated on the SOE.

9 Source Documents

Source documentation is defined as the original documents that serve as the "raw data" for a study and may be in paper or electronic form. Source documents include subject progress notes, laboratory reports, electrocardiograms (EKGs), medication records, X-rays, medical records, hospital records, research clinic records, subjects' diaries, pharmacy dispensing records, recorded data from automated instruments, photographic negatives, and subject files. The eCRFs are not considered source documentation, and should not be used for monitoring purposes to verify study data.

9.1 Demographics

Subject demographics are determined through a self-report, rather than an interpretation by the study staff. It is suggested that the study staff use the source document provided in Appendix 4 to capture the necessary demographics data. The source document should be provided to the subject with instructions for completion. The demographics source document, completed by the subject, should be kept in the subject's research chart. The information from the source document should be entered in the *Demographics* eCRF.

9.2 Clarke Survey

The Clarke survey will be administered at the time points indicated on the SOEs. The survey (with scoring information) is reproduced in Appendix 5. If a subject selects four or more responses coded "R", he or she is determined to have reduced hypoglycemia awareness.

9.3 Blood Sugar Record/Hypoglycemia Sheets

9.3.1 Instructions To Subject

Study coordinators should emphasize to subjects the importance of completing Blood Sugar Record source documents throughout the course of the study because the occurrence of severe hypoglycemic events (events with blood glucose <54 mg/dL [3.0 mmol/L] or requiring someone else's assistance) is a primary endpoint in CIT-06. All hypoglycemic events experienced throughout the study will be entered into the *Blood Sugar Record and Hypoglycemic Events* eCRF.

Study coordinators should also impress upon subjects the importance of filling out the Blood Sugar Record source document as completely as possible and to the best of their ability (see Appendices 5-8). There are two versions of the Blood Sugar Record source document: the white version and the colored version. The white version should be completed for the first three weeks of the month prior to their study visits. On this version of the Blood Sugar Record source documents, a minimum of four blood sugar readings per day must be entered. In the one week prior to their study visits, subjects should complete the *colored* version of the Blood Sugar Record source document. On the colored version of the Blood Sugar Record, seven blood sugar readings per day are required. The form is colored to remind subjects that they should enter a blood glucose reading prior to and approximately 2 hours after each meal, and at bedtime. Coordinators should remind subjects to enter both basal and bolus insulin if they are using an insulin pump.

Additionally, it may be helpful for SCs to contact subjects one week before their scheduled study visits and remind them to fill in the colored Blood Sugar Record source document. An entire 7-day period of blood glucose values and insulin recordings must be provided at these visits, so the subject must begin filling out the colored Blood Sugar Record source document eight days before a study visit. For example, if the visit is scheduled on a Wednesday, the subject should start using the colored record eight days earlier, on Tuesday (see Timing/Scheduling of Metabolic Assessments schematic, Section 8.25).

9.3.2 HYPO Symptom Key

The investigator or coordinator must discuss the subject's entries on the HYPO log with the subject and interpret the nature of each symptom before the symptoms are entered into the *Blood Sugar Record and Hypoglycemic Events* eCRF. The coordinator should consult the HYPO Symptom Key (see Appendix 8) for each hypoglycemic event reported by the subject. This log assists in mapping reported symptoms to scored symptom classes, and the Blood Sugar Record and Hypoglycemic Events eCRF cannot be filled out without the information from the HYPO Symptom Key.

Here are examples of the symptom categories listed on the eCRF and typical examples of symptoms that are encountered for each:

- Autonomic: sweating, shaking, heart palpitations
- Visual: eyes will not focus, impaired vision, diplopia
- Behavior: unable to sleep, irritable, stressed out, nervous, "wanting to sit down and do nothing"
- Other neuro: light-headed, dizzy, weakness, tired, headache, sleepy, difficulty walking or talking, slow responses, delayed motor skills, loss of balance
- Confusion: inability to perform simple math, "out of it"
- Seizures: partial or complete loss of consciousness with or without associated involuntary muscle movements

Points will be assigned based on the occurrence of the event, the recorded blood sugar at the time of the event, the symptoms associated with the event, and the requirement for outside help to recognize or treat the event.

When the subject makes an entry in the "Other" section of the HYPO source document, the coordinator must indicate on the HYPO source document which of the above six categories it falls into, using the HYPO Symptom Key (Appendix 8). An assignment to a symptom category should be noted in the margin of the HYPO source document for each "other" symptom that the subject wrote in.

Because the focus of this measurement is to identify hypoglycemia unawareness, no points are awarded if autonomic symptoms gave adequate warning of impending hypoglycemia, even if some neuroglycopenic symptoms were also present. Hypoglycemic events that are picked up only by meter tests should not be recorded as "needing outside help".

At Visit 03 (yearly) and 365 days post-initial transplant, a full HYPO score will be calculated. This calculation is based on all of the above information plus additional questions that assign points based on the subject's self-report of the number of events in the past year requiring outside help to recognize the event, the number of events in the past year requiring outside help to treat the event, the number of events in the past year requiring administration of glucagon, and the number of events in the past year when an ambulance was called. A source document for collecting this information is included in Appendix 9.

9.4 Retinopathy

At the time of screening, subjects may provide a report from their Ophthalmologist. If a subject has not had an eye exam in the year previous to the time of screening, subjects will be given the document in Appendix 19. Subjects will be instructed to take the form to their scheduled eye exam, request their Ophthalmologist to complete the form, and return the form to the Site SC. Any subsequent retinopathy visits will be conducted in the same manner throughout the study. Please refer to the SOE in the protocol for details regarding the specific time-points when the subjects will complete the retinopathy visits. Data from the source document (Appendix 19) should be entered into the *CIT06 Retinopathy* eCRF.

If in the three months prior to enrollment or at any time after enrollment a subject has laser surgery or a vitrectomy, it is recommended that the subject be considered to have unstable proliferative retinopathy for three months after such event(s).

9.5 Adjudication of Outcomes

Subjects will be asked a series of study outcome questions quarterly (see Appendix 21). These questions will probe for the following events: Myocardial Infarction, Stroke, Renal Failure, and Limb Amputation (above the ankle only). Cardiovascular events are defined in the protocol. When determining renal failure, acute renal events, such as temporary dialysis should not be considered for adjudication, although they should be considered AEs. Dialysis lasting ≥ 60 days will be considered established ESRD.

In the event that an outcome is discovered but an SAE has not been reported, an SAE report must be completed prior to additional adjudication documentation. The Adjudication OUTCOME documentation form (Appendix 22) will be completed and submitted to the Clinical Trial Physician with any additional documentation of the outcome for adjudication. Documentation of the suspected event (hospital summary, PI event summary, etc) should be faxed to the Clinical Trial Physician at the DCC. Additional documentation may be requested by the Clinical Trial Physician and must be supplied by the local center.

Upon adjudication, the DCC will complete the appropriate electronic adjudication form using the data supplied by the local center.

10 Specific eCRF Instructions

10.1 Blood Sugar Record and eCRF

The subject must record blood glucose, hypoglycemic events and insulin usage continuously throughout the study. The PI, or designee, should review the subject's Blood Sugar Record and Hypoglycemia Sheet source documents at each study visit, or more frequently if necessary. Data from these source documents is due at each time-point marked by an "X" on the SOE for the line item "BSR eCRF". The data entered at each specified visit will reflect the subject's blood sugar recordings since their last quarterly visit, including more extensive recordings for the previous 7 days. Blood Sugar Record source documents from all "interim" time periods (between the time-points noted on the SOE) must also be reviewed. All hypoglycemic events from these source documents must be entered into the *Blood Sugar Record and Hypoglycemic Events* eCRF. Entering all hypoglycemic events experienced by a subject while s/he participates is necessary for evaluation of the hypoglycemic events endpoint (see CIT-06 protocol). A source document that can be used as a reminder to query for hypoglycemic events and to confirm that the subject has or has not experienced any events is included in Appendix 16 (HYPO Assessment Sheet).

If a subject returns a completed set of Blood Sugar Record source documents with a limited amount of data collected, the study coordinator should contact his/her DCC protocol coordinator. The DCC protocol coordinator will review the data collected to determine whether it is sufficient to calculate the HYPO, MAGE and LI scores.

Completion of the *Blood Sugar Record and Hypoglycemic Events* eCRF will require reconciliation of the subject's original source document recordings, determination of the subject's actual insulin requirements, and/or inspection of the glucometer download data. The data entered on the eCRFs must exactly match the subject's source documents. The subject's Blood Sugar Record source document is the primary blood sugar source document and should be changed only if absolutely necessary. Coordinators should discuss any discrepancies found among the source documents with the subject. If a change to a source document is required for consistency, the coordinator should initial and date the change. The coordinator's initials and date indicate that s/he has discussed and reconciled the discrepancy with the subject. Individual insulin doses will not be entered into the *Blood Sugar Record and Hypoglycemic Events* eCRF. Instead, the site SC will total the individual doses for each recorded day and enter the daily totals into the *Blood Sugar Record and Hypoglycemic Events* eCRF..

Data entry personnel must enter every blood glucose reading and total daily insulin dose a subject has recorded on his/her Blood Sugar Record and Hypoglycemia Sheet source documents into the *Blood Sugar Record and Hypoglycemic Events* eCRF for the timepoints indicated on the SOE (see above). In addition, ALL hypoglycemic events from all Blood Sugar Records the subject completes must be entered into the *Blood Sugar Record and Hypoglycemic Events* eCRF.

10.1.1 Blood Sugar Records and the Full HYPO Source Document

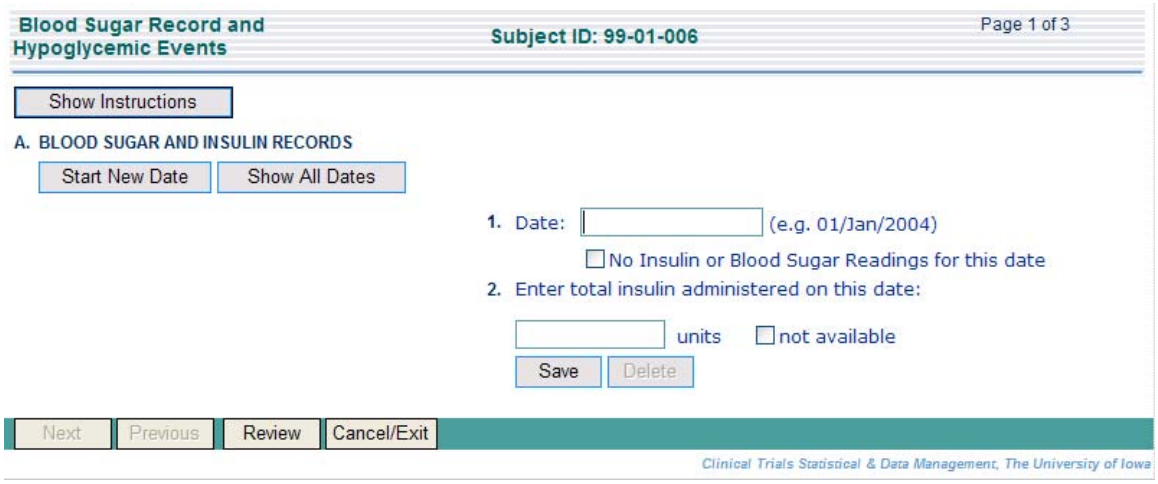
The data from the Blood Sugar Record and HYPO source documents will be entered into the Blood Sugar Record and Hypoglycemic Events eCRF, which is located in the Event-Driven Forms section in each subject's set of eCRFs. All blood sugar records and HYPO events will be added to a growing table that will list all of the blood sugar records and HYPO events recorded

for each subject throughout the study. This is similar to the way lists of concomitant and study medications are maintained in the CIT database for each subject.

The data from the four questions on the Full HYPO Score source document will be entered into the *Full HYPO* eCRF. This eCRF is available at the visits for which Full HYPO data is required. When the *Full HYPO* eCRF is completed, metabolic calculations (HYPO, MAGE and LI scores) will be calculated. For visits at which a Full HYPO eCRF is not required, a modified HYPO score will be calculated, along with the MAGE and LI. Whenever you complete a *Full HYPO* eCRF, please print out a screen shot of the displayed metabolic calculations and add it to the subject's research file. Please note: if you make changes to the entries to the current *Blood Sugar Record and Hypoglycemic Events* eCRF or the *Full Hypo* eCRF (before you have submitted the *Full HYPO* eCRF), the metabolic calculations may change. If you make an update to one of these eCRFs, you should print a screen shot of the new scores to add to the subject's research file.

10.1.2 Entering Dates and Insulin Usage

To start entering blood sugar data on page 1 of the eCRF, click on the "Start New Date" button. In Section A1, enter the first date on the Blood Sugar Record source document. If no blood sugar readings or insulin usage were recorded on that date, click in the checkbox next to "No Insulin or Blood Sugar Readings for this date".

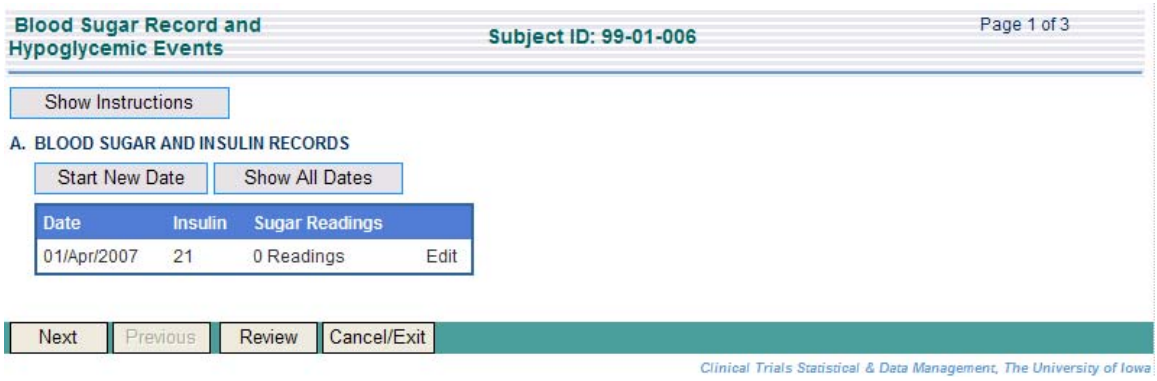


In Section A2, enter the total number of insulin units administered on that date.

If no insulin usage was ***not recorded*** (*i.e.*, all of the insulin blanks on the source document for that day are blank), but there are some blood sugar readings to be entered, click in the checkbox next to "not available".

If the subject is not receiving insulin, insulin should be recorded as 0 units. Enter 0 in the text box next to "units".

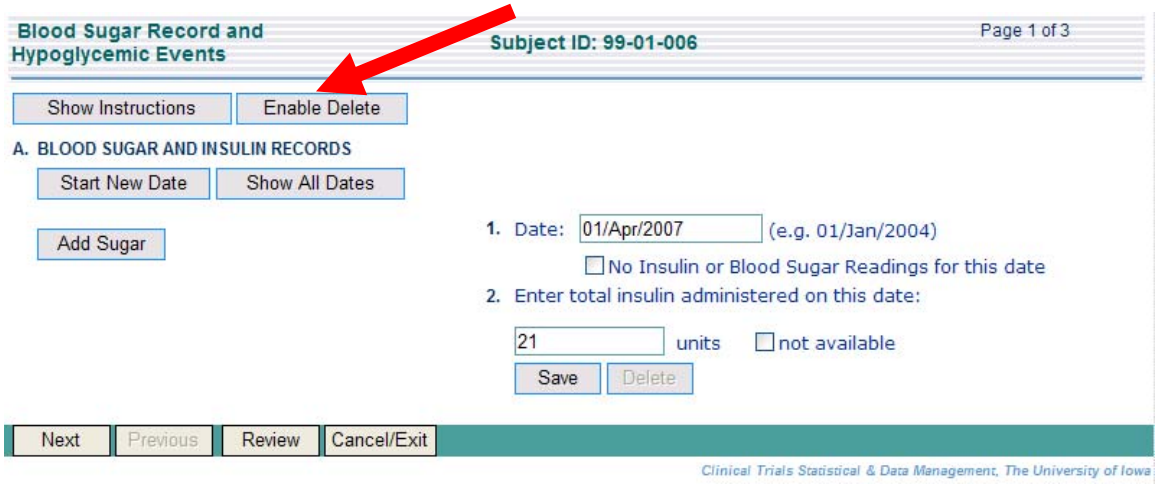
Click the "Save" button under the insulin text box to save this date and insulin entry. The date and insulin usage you entered will be displayed in a table on the left side of the screen. Under the column heading "Sugar Readings", you will see "0 readings" because you have not entered any blood sugar entries yet.



To enter insulin usage on the next date, click the "Start New Date" button above the date/insulin table. The next chronological date will appear in Section A1. Continue with Section A2.

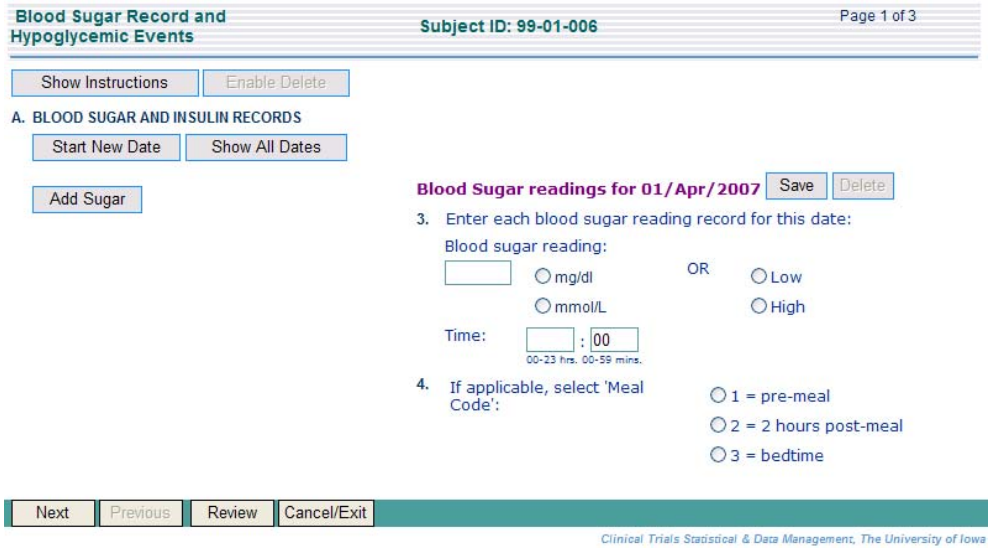
Correcting Errors: If you make a mistake in a date or insulin entry, click on "Edit" in the row for the date on which you need to make changes (in the table displaying the dates and insulin usage). This will take you back to Sections A1 and A2, where you can change your entries. When you are done changing dates/insulin usage, click the button labeled "Show All Dates", and the insulin table displaying the dates and insulin usage will reappear on the left side of the screen.

Deleting a Date/Insulin Record: If you need to delete an entire date, click on "Edit" in the row with the date you need to delete (in the table of dates/insulin usage). Click on the "Enable Delete" button at the top left of the screen. Now click on the "Delete" button in the lower middle of the screen (next to the "Save" button). The entire date and its insulin data will be deleted. The "Delete" button will be grayed out until you click on "Enable Delete".



10.1.3 Entering Blood Sugar Readings

Still on page 1 of the eCRF, to add the blood sugar readings for a date, click on "Edit" in the row for the date on which you want to enter blood sugar readings. Then click on the "Add Sugar" button on the left side of the page. This will bring up Sections A3 and A4 on the right side of the screen.



In Section A3, enter the first blood sugar reading for the date. Select the units: mg/dL or mmol/L. After you select the unit once, it will be filled in for you in future entries. If there is no numerical reading, select "Low" or "High" on the far right side of the screen. Enter the time of the reading in military time. In Section A4, enter the meal code associated with the reading, if applicable. Click the "Save" button above Section A3. A table of the blood sugar readings for this date will appear on the left side of the screen. A3 and A4 will have been cleared, and you can enter the next blood sugar reading there. To return to the table with dates and insulin usage, click the "Show All Dates" button on the left side of the screen.

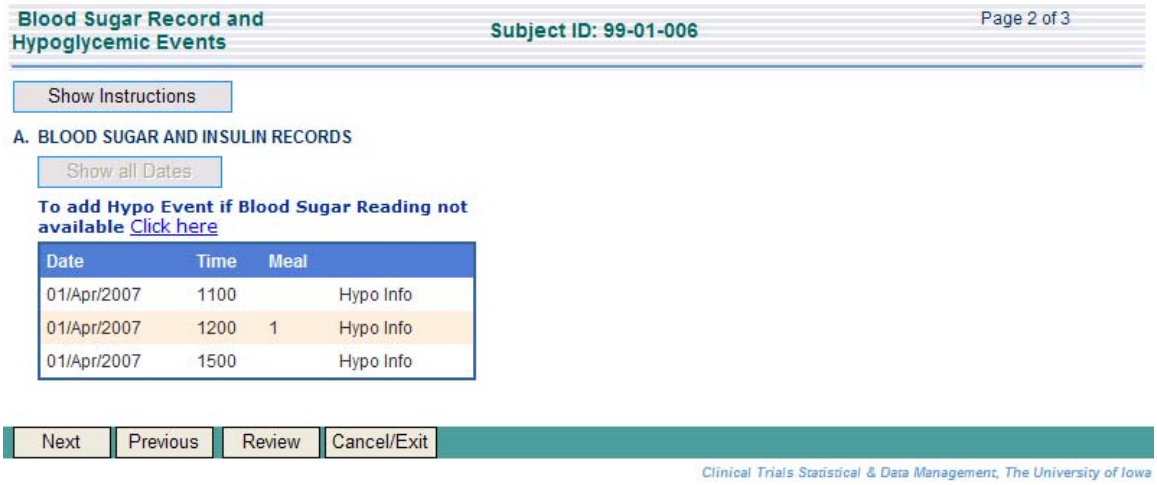
Correcting Errors: If you make a mistake in a blood sugar entry, click on "Edit" in the row with the blood sugar reading you need to change (in the table of blood sugars). Here you will be able to change the blood sugar reading, the time or the meal code. Click the "Save" button when you are done.

Deleting a Blood Sugar Reading: If you need to delete a blood sugar reading, click on "Edit" in the row with the blood sugar reading you need to delete (in the table of blood sugars). Click on the "Enable Delete" button at the top left of the screen. Now click on the "Delete" button at the right side of the screen (next to the "Save" button). The entire blood sugar reading will be deleted. The "Delete" button will be grayed out until you click on "Enable Delete".

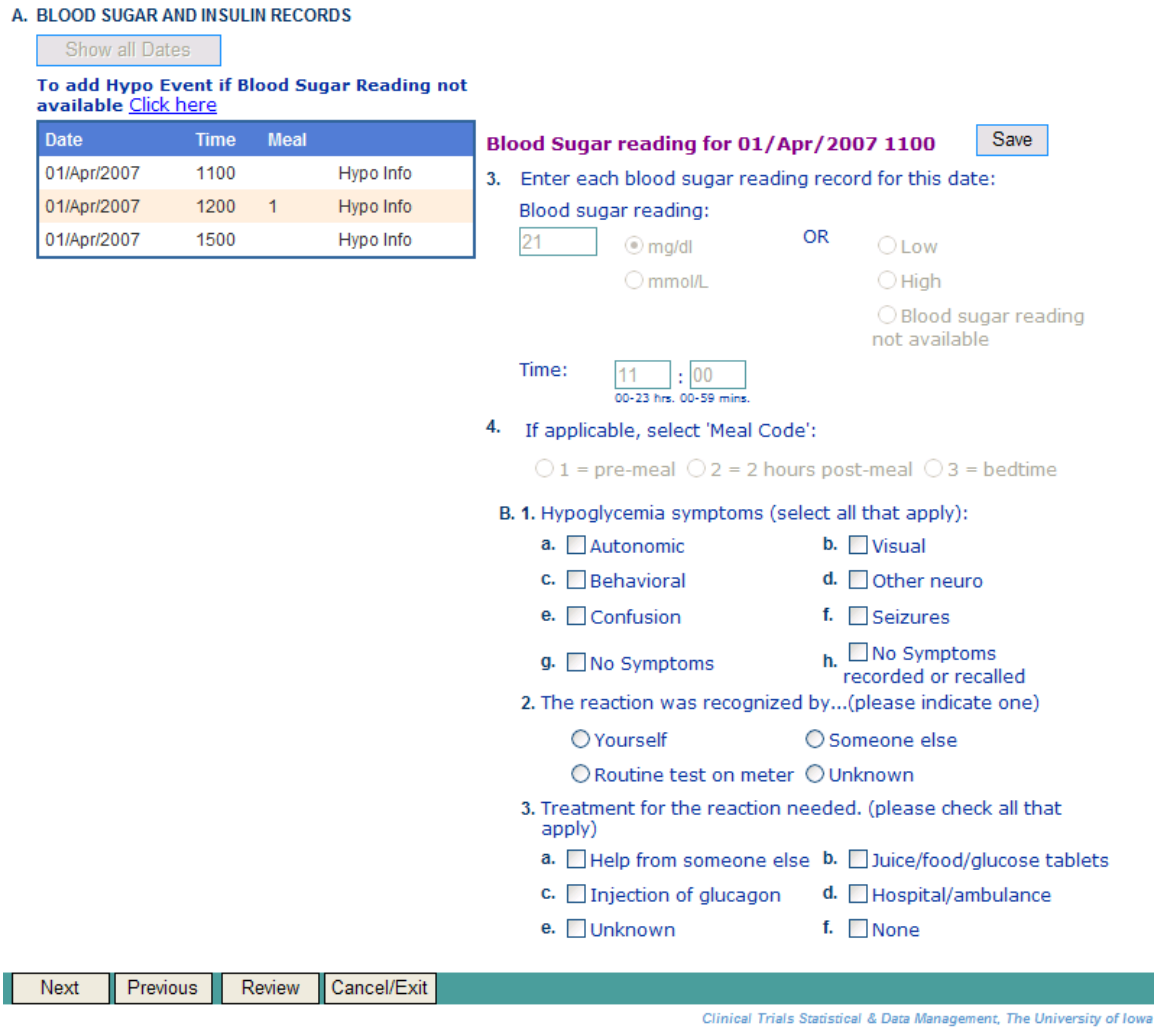
When you have entered all of the blood sugar readings and insulin usage information from the Blood Sugar Record source document, click the "Next" button at the bottom left of the page.

10.1.4 Entering HYPO Info for Blood Sugar Readings

On page 2 of the eCRF, you will see a page with a table of all of the blood sugar readings you entered that were below 54 mg/dL (3.0 mmol/L) or had a "Low" reading.



To enter the HYPO data for a low blood sugar reading, click on "Hypo Info" in the row with the blood sugar reading you want to enter data on. You will be able to see what you entered in Sections A3 and A4, but it will be greyed out, and you cannot change it on this page.



Below Sections A3 and A4, enter the information from the HYPO source documents in Sections B1-B3. When you have entered the HYPO information for one blood sugar reading, scroll up and click the "Save" button to save the HYPO information.

The table of HYPO events will reappear on the left side of the screen, and a small "(Done)" will be displayed next to the HYPO events for which you have entered data.

If a HYPO event is recorded without a blood sugar reading, there is a link to enter that data above the table of HYPO events. Click on "Click Here" to enter HYPO events without blood sugar readings associated with them. You will also have to enter the time of the event in Section A3. When you have entered data for all of the HYPO events recorded on the HYPO source documents, click the "Exit" button at the bottom left of the page.

10.1.5 Entering Full HYPO Score Data

The data from the four questions on the Full HYPO Score source document will be entered into the *Full HYPO Score* eCRF.

10.1.6 Entering Only HYPO Events

All HYPO events must be entered into the Blood Sugar and Hypoglycemic Events eCRF, regardless of whether they are part of one of the official assessments (listed with an X next to "BSR eCRF" on the protocol SOE).

When entering HYPO events only, start by clicking on the Start New Date button. In Section A1, enter the date of the HYPO event. You do not have to enter insulin when you enter HYPO events only, so click "not available" in A2. Then click the Save button.

In order to add the HYPO event, you will need to enter the blood sugar reading associated with the HYPO event. Click on the "Add Sugar" button on the left side of the screen. Fill in Section A3 and click the Save button to save the blood sugar. Enter all of the blood sugar readings associated with HYPO events that you have to enter.

When you have entered all of the blood sugar readings associated with HYPO events, click the Next button in the lower left corner of the screen. This will take you to the second page of the eCRF, where you can enter HYPO information. You will see each of the blood sugar readings you entered in a table on the left side of the screen. Click on "Hypo Info" next to each blood sugar reading to enter HYPO data (as described in Section 10.1.4).

If the subject experienced HYPO events without associated blood sugar readings, click on the "Click here" link above the table where it says, "To add Hypo Event if Blood Sugar Reading not available Click here" (see Section 10.1.4).

When you have entered all of these "interim" HYPO events, click the Exit button at the bottom left corner of the screen.

10.2 Reporting Hypoglycemic Events

Reporting hypoglycemic events is an important part of entering data into the CIT database because freedom from severe hypoglycemic events is a primary endpoint, and the HYPO score is a secondary endpoint in CIT-06.

A severe hypoglycemic event is defined in the CIT-06 protocol as an event with one of the following features: memory loss; confusion; uncontrollable behavior; irrational behavior; unusual difficulty in awakening; suspected seizure; seizure; loss of consciousness; or visual symptoms, in which the subject was unable to treat him/herself and which was associated with either a blood glucose level < 54 mg/dL [3.0 mmol/L] or prompt recovery after oral carbohydrate, IV glucose, or glucagon administration).

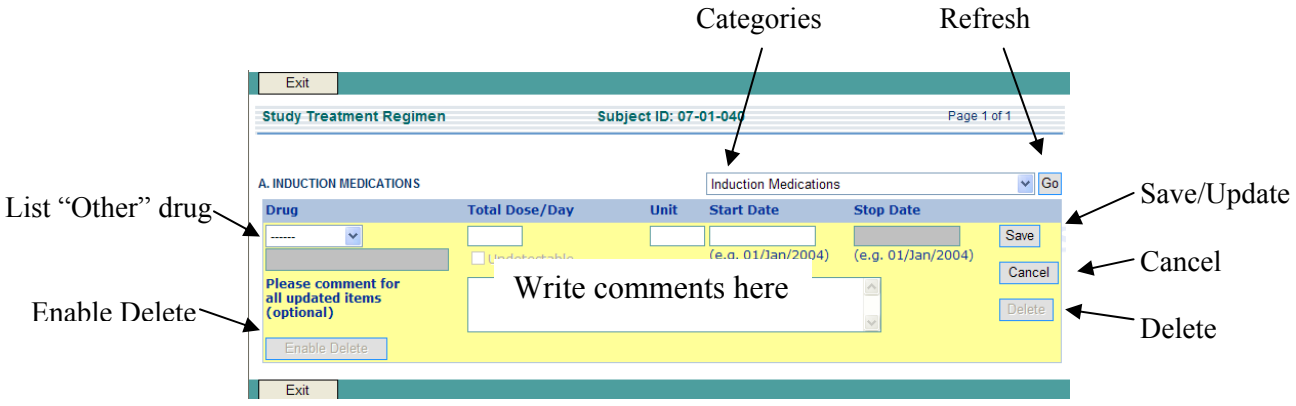
Hypoglycemic events (regardless of severity) may be reported on either or both of two eCRFs:

- *Blood Sugar Record and Hypoglycemic Events* eCRF: **From the time of enrollment, *all* hypoglycemic events (blood glucose <54 mg/dL[3.0 mmol/L]) should be reported on this eCRF**, and the HYPO log should be completed for each event.
- *Adverse Event* eCRF: **From the time of enrollment,** if a subject experiences a hypoglycemic event with any of the characteristics that meet the criteria of **grade 3 severity or higher** (assistance required to treat), the event should be reported on the *Adverse Event* eCRF in addition to the *Blood Sugar Record and Hypoglycemic Events* eCRF. (note: a Grade III or higher hypoglycemic event may or may not meet the definition of a Serious Adverse Event).

10.3 Study Treatment Regimen eCRF

The Study Treatment Regimen (STR) eCRF is located in the Event-Driven Forms section under the Data Collection tab. Drugs administered as part of the Study Treatment Regimen (not including Concomitant Meds) will be added to a table that will grow throughout the study. The table will eventually become a list of all of the study medications taken by the subject for the duration of the study.

The drugs are separated by category of use (induction, maintenance immunosuppression, etc.). The use categories are determined by the study in which a subject is enrolled. Whenever you edit a drug, you must refresh your screen with the "Go" button to continue.



Drug – After you choose a drug category, you must select the drug you wish to enter. If there is only one drug available in that category, the drug will automatically populate into the Drug field. (For example, the only Immunosuppressive/Anti-inflammatory Medication is etanercept; therefore,

etanercept will automatically be selected in the Drug field). If there is more than one drug in a category, you will need to select the correct drug from the drop-down menu under Drug. If "Other" is an option and you select it, the box under the Drug drop-down will become available, and you must enter the name of the new drug.

Total Dose/Day - You will enter the total dose per day that the subject is currently taking. If the subject takes the drug more than once a day, you will add the doses together and enter only one total dose for each day.

Unit - The unit will be automatically populated based upon the drug chosen. If you select "Other", you must enter the units manually.

Start Date - Enter the date the drug, or the current dose of the drug, was started.

Stop Date – Enter the date the drug was discontinued or the last date the dose listed was given. Note: For drugs listed in the following categories: Induction Medication, Immunosuppressive/ Anti-Inflammatory Medication, and Investigational, the Stop date will be greyed out, since the start and stop date will be the same.

Save/Update – After entering the drug name, total dose/day and start date, click on "Save" to save the data. Note – When you are editing an entry by clicking on "Edit", the Save button will change to read "Update".

Cancel – If you enter information in error and wish to return to the previous saved data, click on "Cancel".

Note - The "Delete" button will be greyed out until you click on "Enable Delete".

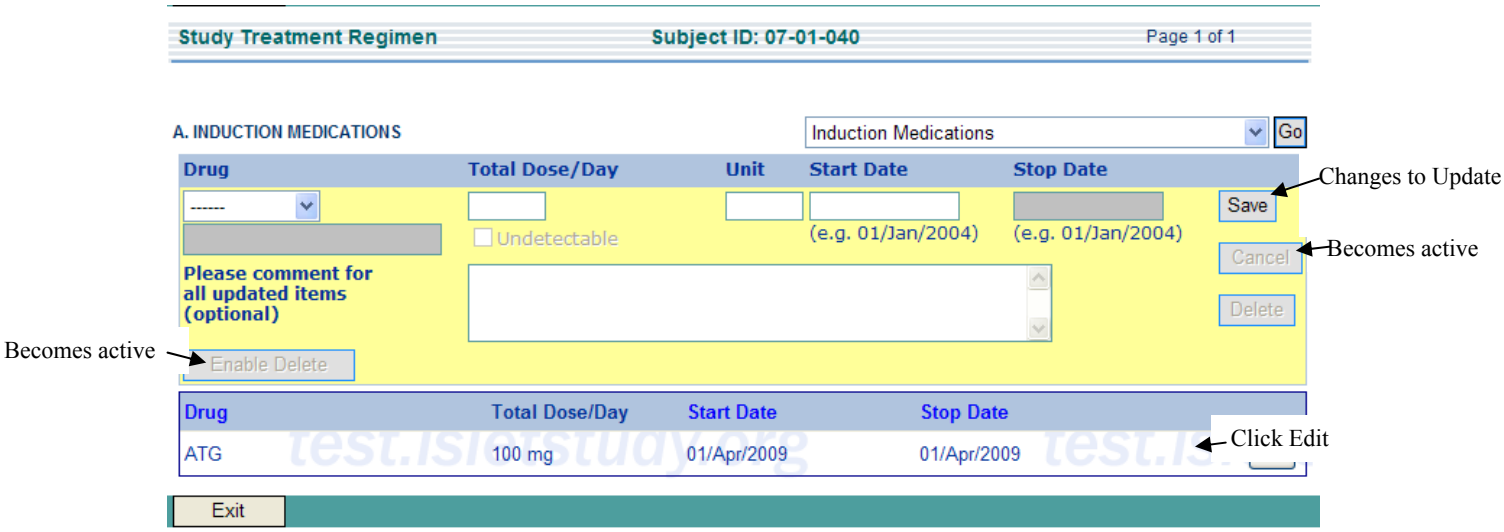
Delete – The delete button is not available until you click on the "Enable Delete" button. If you need to delete a drug, click on "Edit" in the row including the drug you wish to delete. Click on the "Enable Delete" button in the lower left of the screen. Then click on the "Delete" button.

10.3.1 Entering data

1. To start entering data, first select the drug category.
2. Select the drug you wish to enter from the drop-down box.
3. Enter the total dose taken per day.
4. Enter the date the subject started the medication.
5. Click on Save.

A table will begin to grow below the data entry area, listing the all of the medications in the selected category that have been entered.

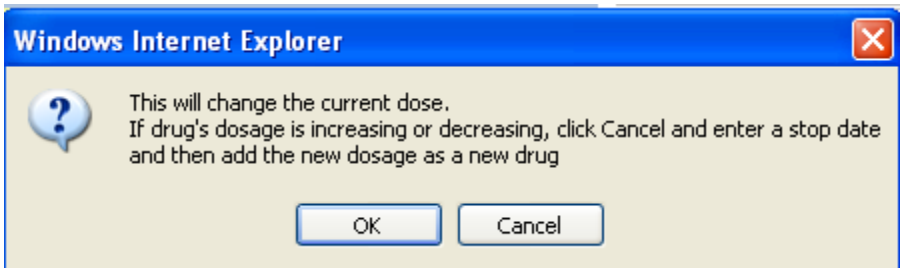
Correcting Errors: If you make a mistake in entering the dose or the date, or you wish to enter a stop date, click on the "Edit" button in the bottom right hand corner.



You will notice that the screen changes. When you click "Edit", the "Save" button becomes "Update", the "Cancel" button is active, and the "Enable Delete" button is active (see above). From here, you are able to make edits and change the dose, or the start date, and save the changes by clicking on "Update". Click "Cancel" if you don't want to make any changes. Click on "Update" after you have corrected the mistake and are ready to save the corrected data. Click on "Enable Delete" and then on "Delete" if you want to delete the drug record completely. Note: You will be prompted to enter a comment to describe the reason for the change.

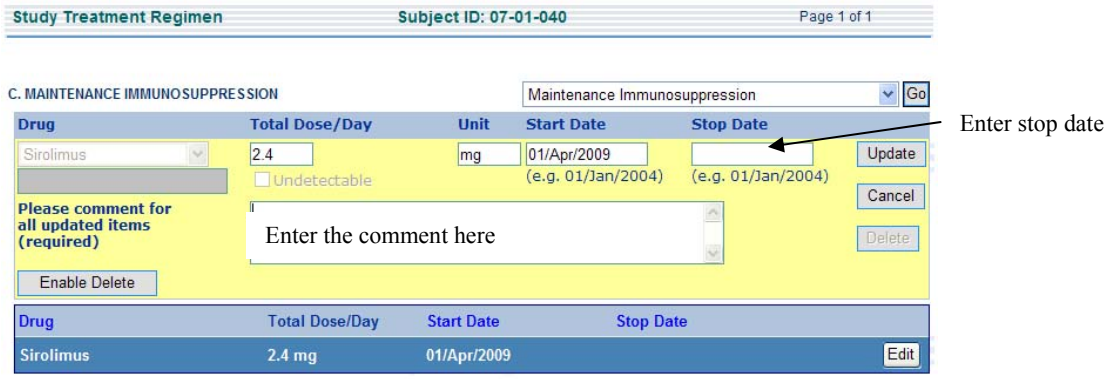
The drugs listed in the following categories: Maintenance Immunosuppression, Infection Prophylaxis Medication, and Anticoagulant Medication do not have the stop date greyed out, since the subject will take these drugs daily. Therefore, the stop date for these drugs must be entered manually. Note: Each drug can only be listed once without a stop date.

Editing a drug with an open stop date - When you edit a drug with an open stop date (stop date not entered), you will receive this message:



If the current dose or date entered is incorrect and you wish to correct the data, enter the correct date or dose, enter a comment for why the change was made and click OK. If the current dose is changing (either increasing or decreasing), click on cancel. Since a drug can only be listed once without a stop date, you must first enter a stop date for the current dose and then enter the drug with the new dose and the new start date.

Changing the dose - For example – this subject was taking Sirolimus 2.4 mg/day on 01/Apr/2009. On 05/Apr/2009, the dose of Sirolimus was increased to 4 mg/day.



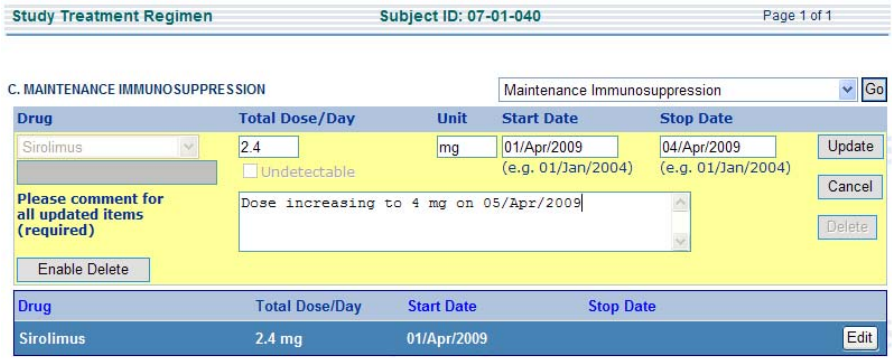
Enter stop date

Click on "Edit" on the line you wish to change.

Enter the stop date of 04/Apr/2009.

Enter a comment – Dose increasing to 4mg on 05/Apr/2009.

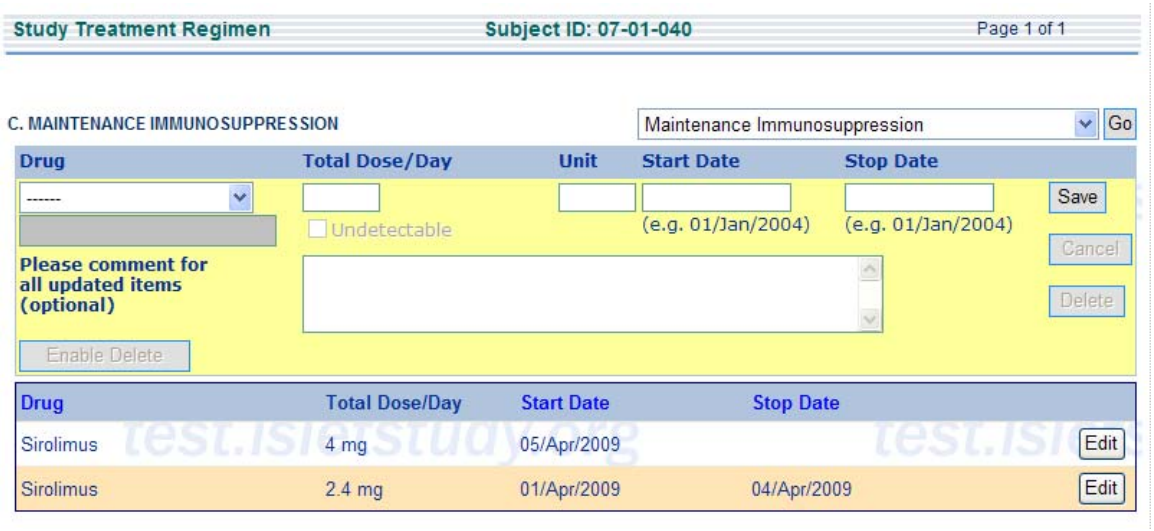
Click on "Update"



Click on "Go" to refresh screen

Enter Sirolimus with new dose of 4mg with start date of 05/Apr/2009.

Click "Save".

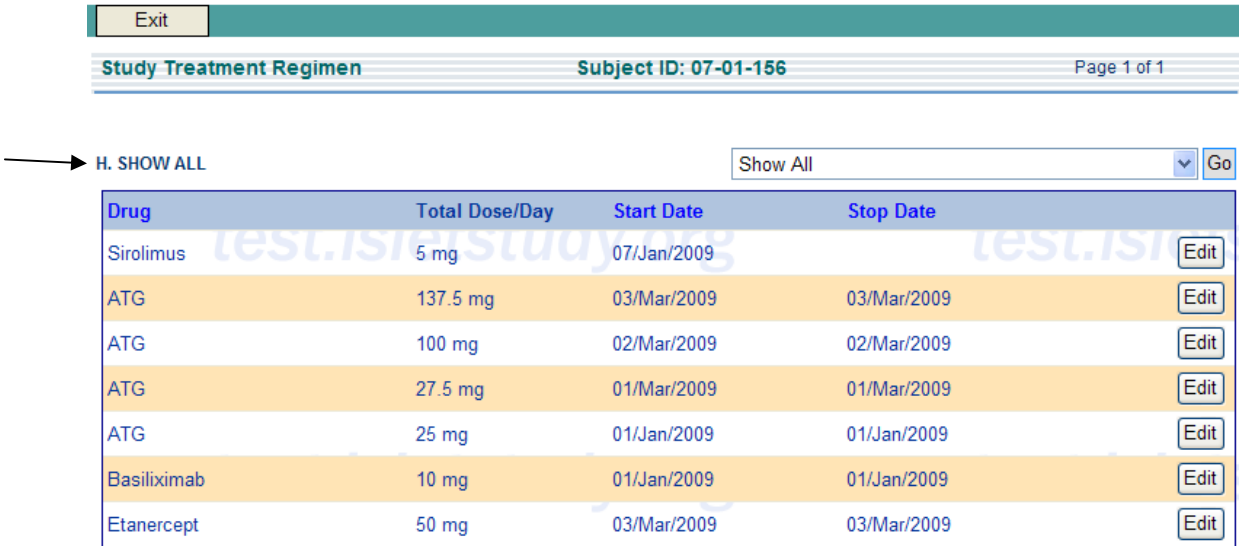


Trough Levels

A trough level can only be entered for a drug that the subject has taken and that has been entered in the STR eCRF. For example, you will not be able to enter a trough level for sirolimus until you have listed sirolimus as a drug the subject has been taking.

Show All

If you wish to see all drugs entered for a subject, go to Show All (in the Drug Category drop-down).



You will see a table that has all of the drugs listed. The columns Drug, Start Date and Stop Date are dark blue. By clicking on any of the column headings, you can sort the drugs. You can also edit any drug from here simply by clicking on the "Edit" button.

10.4 Laboratory eCRF

The laboratory eCRF is divided into sections based on different types of tests: coagulation status, hematology, serum chemistry, thyroid function and fasting lipid panel. If an entire panel or section of tests was not conducted for any reason, the "Not done" box should be checked for the corresponding "Date of draw" question. If part of the panel or section was conducted but a particular component of the test was not done by the laboratory or not reported on the laboratory results, the "Not obtained" box should be checked for the corresponding individual test.

If a blood draw for an individual test is missed or the sample cannot be analyzed and an additional sample is drawn to complete the set of labs, the coordinator should make a Post-Complete Change to the *Laboratory* eCRF containing the rest of the lab results rather than starting an entirely new eCRF. In the "Comments" section of the Post-Complete Change, please note the date of the supplementary draw.

10.5 Concomitant Medications eCRF

Concomitant medications will be collected and entered into the *Concomitant Medications* eCRF following the subject's written consent to participate in the study until study completion, study termination, or until the subject prematurely withdraws from the study.

Study medications listed in the protocol in the "Study Treatment Regimen" section of the protocol should be listed on the *Study Treatment Regimen* eCRF and should not be entered into the *Concomitant Medications* eCRF. All herbals, vitamins and other medicinal products used by or taken by the subject should be entered into the *Concomitant Medications* eCRF. Insulin should not be included as a concomitant medication; please see Section 9.3 for instructions on recording insulin usage.

If ciprofloxacin is administered to a subject during the islet infusion, it should be entered into the *Concomitant Medications* eCRF.

The maintenance immunosuppression taken for the kidney should be entered on the Concomitant Medications eCRF prior to Day = 0 (Visit 05) at which time these medications should be recorded on the *Study Treatment Regimen* eCRF.

10.6 Islet Transplant eCRF

10.6.1 Catheter Introduction Method

The *Islet Transplant* eCRF asks the site to report the "Catheter introduction method" used. Situations may arise where one catheter introduction method is used initially, but the procedure cannot be completed using that particular method. In this case, the investigator may choose to change to a different catheter introduction method. The catheter introduction method used for the actual islet transplant is the one that should be recorded on the eCRF. In the "comments" section of the eCRF, an explanation of why the introduction method was changed should be recorded and an *Adverse Event* eCRF completed, if necessary.

10.6.2 Completion of Islet Transplant

The *Islet Transplant* eCRF asks if the islet transplant was:

- Completely infused without interruption;
- Completely infused with interruption; or

- Not completely infused/prematurely terminated

For the purpose of this eCRF, the term of "interruption" is synonymous with "stopped". A change in rate does not constitute an "interruption", nor does changing of the islet bags if more than one bag is used for the infusion. An "interruption" occurs only if the islet transplant must be stopped either for some period of time or permanently.

11 Reduced Follow-up and Study Termination

11.1 Reduced Follow-Up

Subjects begin the reduced follow-up schedule when they have been withdrawn from study therapy prematurely. Subjects who prematurely discontinue treatment will remain in the study until their treatment would normally have been terminated (3 years post-final transplant). Study coordinators must emphasize to subjects on the reduced follow-up schedule that they must still complete their Blood Sugar Record/Hypoglycemia Sheet source documents for the duration of the follow-up period. Site SCs will make phone contact with subjects on a regular basis to review the content of the completed logs and determine whether the subjects have experienced hypoglycemic events or SAEs (see Reduced Follow-Up SOE in the CIT-06 protocol; the relevant section of the *Reduced Follow-Up* eCRF is reproduced below). Study coordinators should make at least three attempts to contact a reduced follow-up subject for these assessments before considering him/her lost to follow-up.

	No	Yes	
1.	○	○	Has the subject experienced any Serious Adverse Events?
			a. **If yes, then complete the Adverse Event form.**

	No	Yes	
2.	○	○	Has the subject experienced any hypoglycemic events grade 3-4 as defined in the Toxicity Criteria for Adverse Events?
			a. **If yes, then complete the Adverse Event form.**

Additionally, the subject should return to the clinic yearly post-initial transplant for 3 years. Several assessments will be conducted at this visit: PRA, HbA1c, and serum creatinine. If it is not possible for the subject to return to the clinic for this visit, blood for these assessments can be drawn locally and shipped to the clinical center.

Study coordinators must also mail QOL questionnaires to subjects on the reduced follow-up schedule for the yearly post-initial transplant visits (if the subject will not be seen at the clinic for these visits). Questionnaires should be mailed two weeks before the date of the scheduled evaluation, and the subject should be instructed to return the questionnaires by mail if he/she will not be seen at the clinic for the evaluation.

11.2 Study Termination

If a subject is terminated from CIT-06 for reasons of ineligibility during screening or while on WL/BL, and s/he has an "open" (unsubmitted) *Screening Eligibility* or *Transplant Eligibility* eCRF available, the reason for ineligibility should be noted on the appropriate eligibility eCRF rather than on the *Study Termination* eCRF. Completing one of the eligibility eCRFs with a reason for ineligibility will terminate the subject's participation.

If a subject is terminated from a CIT study for other reasons (not related to eligibility) during screening, the coordinator should complete as much of the subject's *Screening Eligibility* eCRF as possible based on data collected up to the point of termination. If some questions on this case report form are not answered, it may be necessary to click the "Validate Page" checkbox at the top right of the page in order to move to the next page of the form. When all the data collected has been entered in the eligibility eCRF, the coordinator should click "Save/Exit". It will not be possible to submit this form to the DCC because it is incomplete. The coordinator should then complete the *Study Termination* eCRF to terminate the subject's participation. This will alert the DCC Protocol Coordinator that the subject has been terminated, and the DCC Protocol Coordinator and the site coordinator will work together to determine what forms should be submitted to close out data collection for the subject.

If a subject is terminated from CIT-06 for reasons that are not related to eligibility during WL/BL, the coordinator should simply complete the Study Termination eCRF. The *Transplant Eligibility* eCRF should, in general, not be accessed until there is an islet prep available for transplant and the coordinator is ready to confirm eligibility for a subject and transplant him/her.

If a subject is terminated after s/he has been transplanted, it is only necessary to complete the *Study Termination* eCRF to terminate his/her participation in the study.

The schematic below is included to help coordinators determine which eCRFs they should complete when a subject must be terminated.

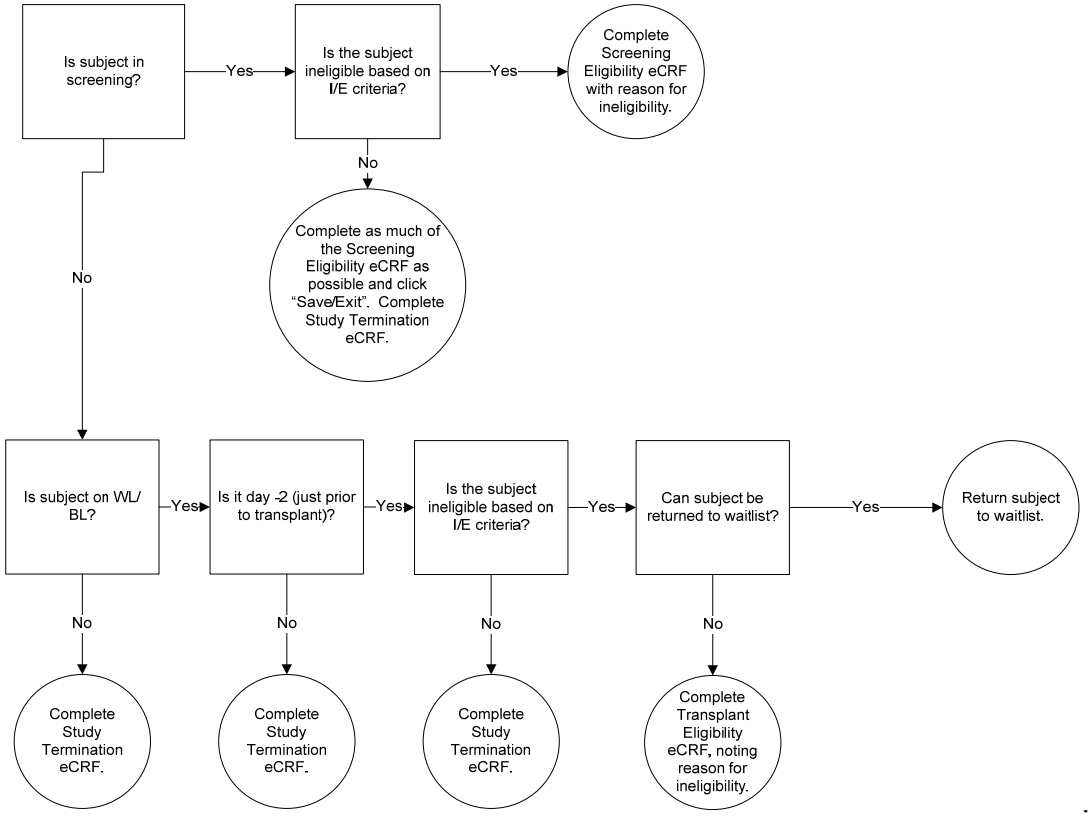


Figure 7: Study termination schematic

If a subject is terminated from a CIT study and subsequently is able to re-enroll (based on eligibility) or wishes to re-enroll (and the PI agrees that the subject can re-enroll), please work with your DCC protocol coordinator to determine whether the subject needs a new subject ID and how to handle data entered prior to the subject's termination.

12 SAE / AE Reporting Procedures and Requirements

For specific information on reporting SAEs and AEs, please refer to the CIT SAE User's Guide and the CIT-06 protocol. For subjects receiving a transplant outside of CIT, please see section 12.3.

12.1 Back-up AE/SAE Reporting Procedures

In the event of failure of the online Adverse Event Reporting System the site should hold all non-serious AEs until the system becomes available (this should not exceed a few hours). When the on-line system is available the site should report all accumulated non-serious AEs in the usual way.

If the online system is not available and the site learns of an SAE, then the site personnel must complete a *"Manual Serious Adverse Event Report Form"* (Appendix 12) and fax it to the DCC Regulatory Coordinator (DCC RC) using the DCC Safety Hotline designated fax number (319-353-4231). The DCC RC will immediately notify the DCC Medical Reviewer that the report has been received. The DCC Medical Reviewer will take responsibility for processing the report, ensuring that it undergoes the appropriate review, and is reported to the appropriate health authority. The DCC RC will be responsible for entering the report in the data base once the system becomes available.

ALL SAEs must be reported immediately within 24 hours after awareness of the event to the Clinical Trial Physician at the DCC using the Data Entry System OR if the electronic data entry is not functioning using the SAE Manual Form.

NOTE: You will need to make copies of the blank *"Manual Serious Adverse Event Report Form"* as needed. Retain originals of all information faxed to the DCC.

12.2 Adverse Event Reporting of Chronic Conditions

12.2.1 Definitions

1. Chronic medical condition (adapted from the CDC definition): A condition that is associated with static or progressive abnormalities that are not expected to resolve once acquired, and which have been present 3 months or longer. Conditions related to pregnancy are NOT considered to be chronic conditions.
2. Worsening/exacerbation of a chronic condition: A change from non-serious to serious, or an increase in severity grade, according to the CIT-TCAE.

12.2.2 Initial Adverse Events Reporting

A new AE should be reported when:

1. A subject with a chronic condition experiences a new sign or symptom that was not previously documented, even though it is recognized as being related to a chronic condition (for example, a subject with pre-existing GERD comes in to the ER to be evaluated for chest pain, which is determined to be related to GERD); OR
2. The subject experiences a worsening or exacerbation of a chronic condition (for example, a subject previously well-controlled hypertension has a hypertensive crisis).

12.2.3 Follow-up Reporting

Changes in seriousness:

1. Changes from non-serious to serious status should be captured via the AE eCRF. Please refer to the *Online Adverse Event Reporting System User's Manual* for detailed instructions. A new initial AE does NOT need to be reported to capture a change in seriousness.
2. Once an event is considered serious, it should remain as serious until resolution.

Changes in severity:

1. The severity grade (using the CIT-TCAE) recorded on the AE eCRF should reflect the highest severity experienced during the course of the event.
2. Increases in severity should be recorded via a post-complete change for non-serious AEs and via a follow-up report for SAEs, as per standard AE eCRF reporting procedures.

12.2.4 Determining Resolution of an AE or SAE Associated with a Chronic Condition

An AE/SAE should be closed when the investigator does not expect any further improvement or worsening. There are two options:

1. The event is considered ***Resolved*** if the subject returns to his/her pre-event status, or better; OR
2. The event is considered ***Resolved with sequelae*** if the subject has stabilized and a new, more severe level of chronic illness persists for three months or more.

12.3 Adverse Event Reporting for Subjects Who Enroll in Non-CIT Studies

A subject who receives an islet transplant in a CIT study and subsequently enrolls in a non-CIT islet transplant study will be followed by the non-CIT study for safety purposes. When the subject begins a non-CIT study intervention, adverse events will no longer be collected in the CIT study. They will be collected only in the non-CIT study. However, the DCC will request copies of any serious adverse events that the subject experiences in the non-CIT study from the CIT principal investigator at regular intervals.

13 Study Supplies

13.1 Accountability

Each clinical site will receive shipments of One Touch Ultra Meters (LifeScan) from Fisher Clinical Services as well as control testing solutions and test strips. Every enrolled subject is provided a meter with supplies for use at home. Sites are to maintain an accountability log of meters, test solutions and test strips (Appendix 10). Additional meters may be ordered by contacting a DCC protocol coordinator. If a meter is non-functional it should be cleaned per institutional standards and returned to:

Clinical Trials Statistical Data Management Center
University of Iowa
2400 UCC
Iowa City, IA 52242

Each clinical site will also receive shipments of CGMSs® (Medtronics) from Fisher Clinical Services including monitors and sensors. Each enrolled subject will be fitted with the monitor and sensor as indicated in the protocol's SOE for 72 hours of continuous glucose monitoring. The data will be downloaded by the sites from the monitors and then uploaded to the DCC (see Section 8.21.1). Upon return of the monitors, the sensors are discarded and the monitors are cleaned per institutional standards. Sites are to maintain an accountability log of meters and sensors (Appendix 11). Additional supplies may be ordered by contacting a DCC protocol coordinator. If a meter is returned to the site it should be cleaned per institutional standards, tested for QC, and then may be used by a new subject. If a CGMS is non-functional, it should be cleaned per institutional standards and returned to the DCC at the address above.

13.2 Study Drugs Available for CIT-06 through Clinical Trials Agreements

No drugs are available to the CIT clinical sites for their CIT-06 subjects through clinical trials agreements.

14 Data Management

14.1 Data Quality Control

The integrity of a study is dependent on the quality of the data submitted. Participating sites enter data into an electronic data entry system. Ownership of the data resides with the site. The DCC has implemented a variety of tools to monitor and report on data quality. The data entry system checks all entries for validity. Values are checked against valid ranges. Any value outside the range is questioned at the time of data entry. Any valid value that is outside the data systems range can be entered into the database but only after the person entering the data confirms that the value is valid. Within form logical consistency is also checked as soon as entry is completed on a given form. Any logical inconsistencies are questioned before data entry can be completed on that form.

The data system also checks for logical consistency between data forms. By necessity, these checks cannot be completed at the time of data entry. Between forms logical checks are run monthly and generate a query list that is sent electronically to the site that entered the data for their review. With the help of DCC staff the site will resolve the logical inconsistencies. The DCC will make the necessary corrections to the database.

The data system will not allow data entry to be completed on a form if any required fields are missing. However, if a data item cannot be obtained (*e.g.,* a sample was lost or was not usable) then the system will allow the value to be flagged as missing in the database and the data value will be considered as completed. Once a data form is completed, the site cannot change values without the approval of the DCC. Any change to a data value that occurs after the site has completed a form is tracked in the data systems audit trail files. The audit trail records the date and time that the change is made, the new value, the old value, and the user ID of the person at the site who is responsible for the change.

14.2 Missing Forms

The data validation process will prompt for missing data forms. The data system will issue an e-mail weekly to each site, detailing forms that are missing and/or forms that have not yet been completed. If a form is overdue by more than one month or has been incomplete for more than one month, the DCC PC will call the site to encourage them to enter the data and complete entry of the form. In the event that data cannot be obtained, the DCC will mark the form as missing in the data system and the site will not be reminded again that the form is missing and/or incomplete.

14.3 Missing Values and Data Anomalies

The purpose of data quality control and missing forms checks is to minimize data anomalies and missing data. However, the data system will allow both missing values and logical inconsistencies after they have been reviewed by the DCC PC and verified as accurate by the site. Algorithms for handling missing data will be described in detail in the statistical analysis plan (SAP).

15 Protocol Compliance

A protocol deviation is defined as a variation from the protocol-directed conduct of a clinical trial. Any noncompliance with the study protocol, GCP, ICH Guidelines, or a protocol-specific MOP requirement is considered a protocol deviation.

It is imperative that the protocol be followed exactly as written whenever possible. If a deviation from protocol-specified procedures is necessary in the interest of ensuring subject safety, the site should treat the subject as clinically necessary and report the deviation to the DCC as described below.

A guide to specific examples of major and minor protocol deviations that could be encountered in CIT-06 is provided in Appendix 15.

15.1 Major Deviations

A major protocol deviation is defined as a deviation that:

1. Impacts the inclusion and/or exclusion criteria;
2. Involves consent violations;
3. Alters protocol-specified study therapy;
4. Impacts the ability of the Sponsor to evaluate the endpoints of the study; or
5. Involves administration of prohibited medications

The sponsor (NIH) is ultimately responsible for determining whether a deviation from the protocol will be reported as major or minor.

All major deviations, regardless of rationale, must be recorded on the *Major Protocol Deviation* eCRF within 24 hours of the site's awareness of the deviation. It is the site's responsibility to report major deviations to the IRB/EC according to site's institutional policy.

15.2 Minor Deviations

Minor deviations are any protocol deviations that are not defined as major deviations (see Section 15.1 above). Examples of minor deviations may include a missed blood draw, a missed visit, a visit occurring outside of the protocol-specified visit window etc. All minor deviations must be recorded, in a timely fashion, on a *Minor Protocol Deviation* eCRF.

15.3 Deviations from Protocol-Directed Therapy

In some instances, there is acknowledgment in the protocol that a therapy might not be tolerated, requiring the treating physician to modify the therapy, as in the following example from CIT-06:

5.3.2.1 TRIMETHOPRIM/SULFAMETHOXAZOLE (SEPTRA SS®/BACTRIM®)
Trimethoprim / sulfamethoxazole will be administered at a dose of 80 mg/400 mg PO QD starting on Day +1 for 6 months after islet transplant for the prevention of Pneumocystis carinii. In the event that a subject is unable to take trimethoprim/sulfamethoxazole, he/she will be treated on a case-by-case basis as is medically indicated.

In these instances, the physician should document in the medical record that the protocol-directed therapy was not tolerated and describe the alternative to be administered to the study subject. This situation does not require that a protocol deviation be reported.

In the absence of protocol language specifically authorizing treatment on a case-by-case or individualized basis, all other departures from protocol-directed therapy, even if undertaken in the subject's best interest, must be reported as protocol deviations.

References

1. Mazurek G, Jereb J, Lobue P, Iademarco M, Metchock B, Vernon A. Guidelines for using the QuantiFERON-TB Gold test for detecting Mycobacterium tuberculosis infection, United States. *MMWR Recomm Rep.* 2005;54((RR-15)):49-55.

2. Green M, Avery R, Preiksaitis JE. Guidelines for the prevention and management of infections complications of solid organ transplantation. *Am J Transplant.* 2004;4(S10).

3. Preiksaitis J, Brennan D, Fishman J, Allen U. Canandian Society of Transplantation Consensus Workshop on Cytomegalovirus Management in Solid Organ Transplantation Final Report. *Am J Transplant.* 2005;5:218-227.

4. Hirsch H, Brennan D, Drachenberg C, et al. Polyomavirus-Associated Nephropathy in Renal Transplantation: Interdisciplinary Analyses and Recommendations. *Transplantation.* 2005;79(10):1277-1286.

Appendix 1 DSMB Charter

Clinical Trials Involving Islet/beta Cell Transplantation Sponsored by NIDDK

The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to NIDDK to monitor subject safety, evaluate the efficacy of the intervention and evaluate significant changes in protocols. All grants involving clinical trials involving islet/beta cell transplantation sponsored will be reviewed by this DSMB. A trial co-sponsored by NIDDK may be reviewed by this DSMB or by a comparable DSMB run by another co-sponsoring organization.

DSMB RESPONSIBILITIES

The initial responsibility of the DSMB will be to review the research protocol, informed consent documents and plans for data safety and monitoring and to approve the initiation of this clinical trial. For this initial evaluation, if there has been a significant change from the original grant specific aims, a scientific review will also be made and recommendations will be provided to NIDDK regarding the safety and scientific value of the proposed changes. After an approval, and at periodic intervals (to be determined) during the course of the trial, the DSMB responsibilities are to:

- review changes in the research protocol, informed consent documents and plans for data safety and monitoring;
- evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial site, and other factors that can affect study outcome;
- consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- protect the safety of the study participants;
- report on the safety and progress of the trial;
- make recommendations to the NIDDK, the PI, and, if required, to the Food and Drug Administration (FDA) and the Institutional Review Board (IRB) concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- if appropriate, conduct interim analysis of efficacy in accordance with stopping rules which are clearly defined in advance of data analysis and have the approval of the DSMB;
- ensure the confidentiality of the trial data and the results of monitoring;

- and, assist NIDDK by commenting on any problems with study conduct, enrollment, and sample size and/or data collection;
- evaluate any significant changes in the specific aims of the grant occurring after the initial review by the DSMB and make recommendations to NIDDK regarding the safety and scientific value of the proposed changes.

MEMBERSHIP

The DSMB will consist of at least eight members. Five members will constitute a quorum. NIDDK has approved the composition of the DSMB, and appointed the members. Membership consists of persons completely independent of the investigators who have no financial, scientific, or other conflict of interest with the trials. Collaborators or associates of grant principal investigators are not eligible to serve on the DSMB. Written documentation attesting to absence of conflict of interest is required. Should a conflict arise with a specific protocol, the conflicted member(s) will be recused from the discussion and evaluation of that protocol. Should specific expertise be required for the evaluation of a protocol, ad hoc members can be added to fulfill this need. The DSMB includes experts in or representatives of the fields of:

- Adult/Pediatric endocrinology
- Biostatistics/ Clinical trial methodology
- Pancreatic islet transplantation
- Ethics
- Subject representation
- Transplant surgery/medicine

Robert Sherwin, M.D., has been selected by NIDDK to serve as the Chairperson. He is responsible for overseeing the meetings and developing the agenda in consultation with the NIDDK Program Official. Jerry Palmer, M.D. is the co-chair who will act as the Chairperson in Dr. Sherwin's absence. The NIDDK Official, Thomas L. Eggerman, will serve as the Executive Secretary (ES) and is the initial contact for the DSMB. The chair is the official contact person for the DSMB. NIDDK shall provide the logistical management and support of the DSMB.

A Safety Officer for each grant will be identified by the PIs at the first meeting. This person will be the contact person for severe adverse event reporting. Procedures for notifying the Chair of the DSMB and the NIDDK Program Official will be discussed at the first meeting.

BOARD PROCESS

The first meeting will take place face-to-face to discuss the protocol, any modifications of the trial, and to establish guidelines to monitor the study. The NIDDK Program Official, the DSMB Chairperson will prepare the agenda to address the review of manual of operating procedures, modification of the study

design, initiation of the trial, identification of a safety officer, reporting of adverse events, stopping rules, interim analysis plan, etc.

Meetings of the DSMB will be held two times a year at the call of the Chairperson, with advance approval of the NIDDK Program Official. Meetings may be convened as conference calls as well as in person, although the initial meeting and meetings to discuss interim analysis will be face-to-face. An emergency meeting of the DSMB may be called at any time by the Chairperson or by NIDDK should questions of subject safety arise. A NIDDK Official(s) will be present at every meeting.

Meetings shall be closed to the public because discussions may address confidential subject data. Meetings may be attended by the principal investigator and members of his/her staff when necessary.

MEETING FORMAT

An appropriate format for DSMB meetings consists of an open and a closed session. The open sessions may be attended by the principal investigator(s), institution staff and NIDDK staff. Issues discussed at open sessions will include conduct and progress of the study, including subject accrual, compliance with protocol, and problems encountered. Subject-specific data and treatment group data may not be presented in the open session.

The closed session will be attended only by voting DSMB members and the NIDDK ES. The DSMB may request others to attend a part or all of the closed session (e.g., study statistician, NIDDK staff). All safety and efficacy data are and must be presented at this session. The discussion at the closed session is completely confidential.

Should the DSMB decide to issue a termination recommendation, full vote of the DSMB will be required. In the event of a split vote, majority vote will rule and a minority report should be appended.

REPORTS

1. **Interim Reports:** Interim reports are generally prepared by the study statistician(s) and distributed to the DSMB at least 10 days prior to a scheduled meeting. These interim reports are numbered and provided in sealed envelopes within an express mailing package or by secure email as the DSMB prefers. The contents of the report are determined by the DSMB. Additions and other modifications to these reports may be directed by the DSMB on a one-time or continuing basis. Interim data reports generally consist of two parts:

   Part 1 (Open Session Report) provides information on study aspects such as accrual, baseline characteristics, and other general information on study status.

   Part 2 (Closed Session Report) may contain data on study outcomes, including safety data, and depending on the study, perhaps efficacy data. The Closed Session Report is considered confidential and should be destroyed at the conclusion of the meeting. Data files to be used for interim analyses should have undergone established editing procedures to the extent

possible. Interim analyses of efficacy data are performed only if they are specified and approved in advance and criteria for possible stopping is clearly defined.

2. Reports from the DSMB: A formal report containing the recommendations for continuation or modifications of the study prepared by the ES with concurrence from the DSMB Chairperson will be sent to the full DSMB within 4 weeks of the meeting. Once approved by the DSMB, the NIDDK will forward the formal DSMB recommendation report to the PI. It is the responsibility of the PI to distribute the formal DSMB recommendation report to all co-investigators and to assure that copies are submitted to all the IRBs associated with the study.

As previously stated, the formal DSMB report should conclude with a recommendation to continue or to terminate the study. This recommendation should be made by formal majority vote. A termination recommendation may be made by the DSMB at any time by majority vote. The NIDDK is responsible for notifying the PI of a decision to terminate the study. In the event of a split vote in favor of continuation, a minority report should be contained within the regular DSMB report. The report should not include unblinded data, discussion of the unblinded data, etc.

Mailings to the DSMB: On a scheduled basis (as agreed upon by the DSMB) blinded safety data should be communicated to all DSMB members or to the designated safety officer (to be determined at the first meeting). Any concerns noted should be brought to the attention of the DSMB Chairperson or designated safety officer and the NIDDK Program Official.

Access to Interim Data: Access to the accumulating endpoint data should be limited to as small a group as possible. Limiting the access to interim data to the DSMB members relieves the investigator of the burden of deciding whether it is ethical to continue to randomize subjects and helps protect the study from bias in subject entry and/or evaluation.

CONFIDENTIALITY

All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

Appendix 2 Procedures for Determining Eligibility of a Subject for Enrollment to the Islet After Kidney Protocol

Background: The intent of the eligibility criteria is to limit entrance of subjects into this protocol to those people who are unable to achieve a satisfactory blood glucose control without an excessive risk of hypoglycemic episodes or wide blood glucose swings. The CIT-06 Protocol embodies this intent in Inclusion Criterion #7. To assure that entry is limited to subjects in this specific high risk group, and to minimize the possibility of entering a subject not meeting this criterion, the study has chosen to require that an endocrinologist or diabetes specialist not associated with the transplant team at a given subject's center attest to the fact that the subject meets this criterion. There are two ways in which this requirement may be met.

a. In some cases, the subject will have been under the care of an endocrinologist or diabetes specialist not responsible for subject care on the CIT protocols prior to inquiring about the trial. When such a subject is seen at one of the CIT Clinical Centers, appears to have met general trial eligibility criteria, and has signed consent, the subject will be instructed in completion of the questionnaire that is needed for the computation of the Clarke Score. Upon completion of the questionnaire, the Center will do the calculation needed for the score. The record will then be mailed to the subject's private endocrinologist/diabetologist with a copy of the letter and questionnaire attached, with the request that the outside doctor complete and return the questionnaire to the CIT Clinical Center. In this case, the affirmative answers on the questionnaire, signed by the outside doctor, will serve as the confirmation that the subject meets eligibility criterion 7.

b. In some cases, the subject will receive his/her diabetes care from a physician at the CIT Clinical Center who is an active member in the CIT protocols. In other cases, it may be that the subject's outside endocrinologist/diabetologist may fail to or decline to complete and return the above questionnaire. To deal with this eventuality, the study will appoint an Eligibility Committee of at least three endocrinologists/diabetologists participating in the CIT Studies from at least three different institutions. A summary of the subject's medical records will be forwarded to the members of the Committee (with identifiers blacked out). The members of the Committee not from the referring CIT Center will review the records, and may request additional information as needed. They will then vote on whether the subject meets the entry criteria. Two of 3 positive votes if all members are eligible to vote, or 2/2 if one member is from the referring CIT Center, will be considered a positive vote for eligibility. A positive vote of this committee will serve as the confirmation that the subject meets eligibility criterion 7. To speed resolution of these questions, the required documents will be forwarded by the referring CIT center to the DCC, which will then distribute the required documents to the committee members. The Committee may meet in person, by conference call, or by e-mail ballot (messages sent to Dr. Hunsicker at the CIT Data Center or his surrogate), and the DCC will report the outcome to the referring CIT Clinical Center.

Dear Dr. _____:

We had the pleasure of seeing your subject, _____, as part of an evaluation for islet after kidney transplantation. Islet after kidney transplantation is an experimental therapeutic option for selected type 1 diabetic subjects who have had a previous kidney transplant and who are experiencing frequent problems with hypoglycemia despite adherence to an optimal insulin regimen. Islet after kidney transplantation at the [name of institution] is being performed under a research study sponsored by the National Institutes of Health. All eligible subjects will be listed for and may receive an islet transplant. If you are interested in more information about this study, please visit our website at http://www.isletstudy.org or call us at the numbers listed below. We encourage you and your subject to discuss the intent and the specifics of the research protocol.

_____ has completed his/her eligibility evaluation, and we would greatly appreciate if you could confirm the attached criteria that relate to his/her diabetes history, present treatment, and difficulty with hypoglycemia. Upon enrollment, we calculated a Clarke score of _____, indicating reduced awareness of hypoglycemia. Please complete and sign the attached checklist and return in the envelope provided.

Thank you very much for your time and consideration of this request. We will keep you informed of _____ status in the islet after kidney transplantation program.

Sincerely,

CIT Physician
Address
Phone #
Email address

Subject Name: _____

1.) Did your subject have onset of Type I diabetes prior to age 40 years?

Yes _____ No _____

2.) Has your subject been insulin-dependent for more than 5 years?

Yes _____ No _____

3.) Has your subject been under the management of an endocrinologist, diabetologist, or other diabetes specialist for at least one year, with at least three clinical evaluations over this past year?

Yes _____ No _____

4.) Has your subject followed for at least one year a program of intensive diabetes management, including:

a. Self monitoring of blood glucose at least three times daily on average, AND
b. Administration of three or more injections of insulin daily on average or use of an insulin pump

Yes _____ No _____

5.) Has your subject been UNABLE to achieve glycemic control without hypoglycemic episodes (HbA1c > 7.5%, or HbA1c <7.5% but with reduced awareness of hypoglycemia)?

Yes _____ No _____

6.) Has your subject had in the past year at least one severe hypoglycemic event (requiring assistance of another person, and with measured blood glucose < 54 mg/dL [3.0 mmol/L] and/or prompt recovery after administration of carbohydrate or glucagon)?

Yes _____ No _____

Signed _____ Date _____

Appendix 3 Diabetes Specialist Questionnaire

Clinical Islet Transplantation Consortium

Documentation of Qualification as a Diabetes Specialist

Name:

Address:

Telephone number:

Medical license #:_____ **State:** _____

Board certified or qualified in Adult/Pediatric Endocrinology: ( ) Yes ( ) No

If no, then do you have experience in the management of type 1 diabetes by:

a. prescription and management of insulin pumps: ( ) Yes ( ) No

b. prescription and management of intensive insulin regimens (long acting basal insulin plus short acting prandial insulin at least three times daily):

( ) Yes ( ) No

Is a Certified Diabetes Educator a part of your management team?

( ) Yes ( ) No

Appendix 4 Demographics Source Document

Subject Name: _____

Subject ID Number: CIT ___ ___ - ___ ___ - ___ ___ ___

Ethnicity

1. Do you consider yourself to be Hispanic or Latino? (See definition below.) Select one.

   Hispanic or Latino. A person of Mexican, Puerto Rican, Cuban, South or Central American, or other Spanish culture or origin, regardless of race. The term, "Spanish origin," can be used in addition to "Hispanic or Latino."

   ☐ Hispanic or Latino

   ☐ Not Hispanic or Latino

Race

2. What race do you consider yourself to be? Select one or more of the following.

   ☐ ***American Indian or Alaska Native.*** A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliation or commuity attachment.

   ☐ ***Asian***. A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Phillippine Islands, Thailand, and Vietnam. (Note: Individuals from the Phillippine Islands have been recorded as Pacific Islanders in previous data collection strategies

   ☐ ***Black or African American.*** A person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black" or "African American."

   ☐ ***Native Hawaiian or Other Pacific Islander.*** A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

   ☐ ***White.*** A person having orgins in any of the original peoples of Europe, the Middle East, or North Africa.

   ☐ Check here if you do not wish to provide some or all of the above information.

Appendix 5 Clarke Survey

Hypoglycemia Clinical Symptom Questionnaire

Subject ID: ___ ___ - ___ ___ - ___ ___ ___
Date: __/__/__

INSTRUCTIONS TO COORDINATOR: Please ask the subject the appropriate question (A, B, **or** C) according to their current visit. **If their answer is "no", do not fill out the remainder of the survey. If their answer is "yes", proceed to question #1 and complete the survey.**

A. Screening Visit: "Have you experienced any hypoglycemia in the past 12 months?" Yes No
B. Wait List: "Have you experienced any hypoglycemia in the past 6 months?" Yes No
C. Post Transplant: "Have you experienced any hypoglycemia since your last visit?" Yes No

---

1) Check the category that best describes you: (check one only)
_____ I always have symptoms when my blood sugar is low
_____ I sometimes have symptoms when my blood sugar is low
_____ I no longer have symptoms when my blood sugar is low

2) Have you lost some of the symptoms that used to occur when your blood sugar was low?
___ yes ___no

3) In the past 6 months how often have you had hypoglycemia episodes where you felt confused, disoriented, or lethargic and were unable to treat yourself?

___Never ___Once or twice ___Every other month ___Once a month ___More than once a month

4) In the past 12 months how often have you had hypoglycemia episodes where you were unconscious or had a seizure and needed glucagon or intravenous glucose?

___Never ___1 time ___2 times ___3 times ___5 times ___6 times ___7 times

___8 times ___9 times ___10 times ___11 times ___12 or more times

5) How often, in the last month, have you had readings less than 70 mg/dl (3.9 mmol/L) with symptoms?

___Never ___1-3 times ___1 time/week ___2-3 times/week ___4-5 times/week ___almost daily

6) How often in the last month have you had readings less than 70 mg/dl (3.9 mmol/L) without symptoms?

___Never ___1 - 3 times ___1 time/week ___2 - 3 times/week ___4 - 5 times/week ___Almost daily

7) How low does your blood sugar go before you feel symptoms?
___60 - 69mg/dl (3.3 – 3.8 mmol/L) ___50 - 59mg/dl (2.8 – 3.2 mmol/L) ___40 - 49 mg/dl (2.2 – 2.7 mmol/L)
___< 40 mg/dl (2.2 mmol/L)

8) To what extent can you tell by your symptoms that your blood sugar is low?

___ Never ___Rarely ___Sometimes ___Often ___Always

Scoring Key for Hypoglycemia Clinical Symptom Questionnaire (Clarke Survey)

SCORING KEY

1) Check the category that best describes you: (check one only)
_____ I always have symptoms when my blood sugar is low (A)
_____ I sometimes have symptoms when my blood sugar is low (R)
_____ I no longer have symptoms when my blood sugar is low (R)

2) Have you lost some of the symptoms that used to occur when your blood sugar was low?
___ yes (R) ___no (A)

3) In the past 6 months how often have you had hypoglycemia episodes where you felt confused, disoriented, or lethargic and were unable to treat yourself?
___Never (A) ___Once or twice (R) ___Every other month (R) ___Once a month (R)
___More than once a month (R)

4) In the past 12 months how often have you had hypoglycemia episodes where you were unconscious or had a seizure and needed glucagon or intravenous glucose?
___Never (A) ___1 time (R) ___2 times (R) ___3 times (R) ___5 times (R) ___6 times (R)
___7 times (R) ___8 times (R) ___9 times (R) ___10 times (R) ___11 times (R)
___12 or more times (R)

5) How often, in the last month, have you had readings less than 70 mg/dl (3.9 mmol/L) with symptoms?
___Never ___1-3 times ___1 time/week ___2-3 times/week ___4-5 times/week
___almost daily

6) How often in the last month have you had readings less than 70 mg/dl (3.9 mmol/L) without symptoms?
___Never ___1-3 times ___1 time/week ___2-3 times/week ___4-5 times/week
___Almost daily

(Score as R if the answer to 5 < answer to 6. Score as A if the answer to 5 > answer to 6. When answers to 5 and 6 are the same, A=Never/Never, R=any other set of responses)

7) How low does your blood sugar go before you feel symptoms?
___60 - 69mg/dl [3.3 – 3.8 mmol/L] (A) ___50 - 59mg/dl [2.8 – 3.2 mmol/L] (A)
___40 - 49 mg/dl [2.2 – 2.7 mmol/L] (R) ___< 40 mg/dl [2.2 mmol/L] (R)

8) To what extent can you tell by your symptoms that your blood sugar is low?
___ Never (R) ___Rarely (R) ___Sometimes (R) ___Often (A) ___Always (A)

Four or more R responses = reduced awareness; 2 or fewer R responses = aware

Appendix 6 Blood Sugar Record/Hypoglycemia Sheet and Instructions (International)

Blood Sugar Record and HYPO Log (International) **NAME** ________________________________ SUBJECT ID __ __ - __ __ - __ __ __

Record your blood sugar a minimum of 4 times per day and number of insulin units taken daily. **Record Meal Code: 1=pre-meal, 2=2 hours post-meal, 3=bedtime**

Date: Total Insulin

Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Meal Code																									

Date: Insulin

Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Meal Code																									

Date: Insulin

Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Meal Code																									

Date: Insulin

Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Meal Code																									

Date: Insulin

Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Meal Code																									

Date: Insulin

Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Meal Code																									

Date: Insulin

Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Meal Code																									

For every reading below 3.0 mmol/L or a hypoglycemic event requiring the assistance of another, please record details on Hypoglycemia Sheet (see reverse)

Blood Sugar Record and HYPO Log (1 WEEK PRIOR TO VISIT) **NAME** ______________________________ SUBJECT ID __ __ - __ __ - __ __ __

Record your blood sugar a minimum of 7 times per day and number of insulin units taken daily. **Record Meal Code: 1=pre-meal, 2=2 hours post-meal, 3=bedtime**

Date:						Breakfast (Pre and 2 hr. post)					Lunch (Pre and 2 hr post)					Dinner (Pre and 2 hr post)					Bedtime				Total Insulin
Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Meal Code																									

Date:						Breakfast (Pre and 2 hr. post)					Lunch (Pre and 2 hr post)					Dinner (Pre and 2 hr post)					Bedtime				Insulin
Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Meal Code																									

Date:						Breakfast (Pre and 2 hr. post)					Lunch (Pre and 2 hr post)					Dinner (Pre and 2 hr post)					Bedtime				Insulin
Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Meal Code																									

Date:						Breakfast (Pre and 2 hr. post)					Lunch (Pre and 2 hr post)					Dinner (Pre and 2 hr post)					Bedtime				Insulin
Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Meal Code																									

Date:						Breakfast (Pre and 2 hr. post)					Lunch (Pre and 2 hr post)					Dinner (Pre and 2 hr post)					Bedtime				Insulin
Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Meal Code																									

Date:						Breakfast (Pre and 2 hr. post)					Lunch (Pre and 2 hr post)					Dinner (Pre and 2 hr post)					Bedtime				Insulin
Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Meal Code																									

Date:						Breakfast (Pre and 2 hr. post)					Lunch (Pre and 2 hr post)					Dinner (Pre and 2 hr post)					Bedtime				Insulin
Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Meal Code																									

For every reading below 3.0 mmol/L or a hypoglycemic event requiring the assistance of another, please record details on Hypoglycemia Sheet (see reverse)

Hypoglycemia Sheet

If you need more space, please copy an extra sheet

Date:____________________ Time:__________________ Blood Sugar Value:____________________

Symptoms felt or what did you notice? (Please circle all symptoms noticed)

sweating problems with vision other: ____________________________ **OR** NONE
shaking change in behavior ____________________________________
heart palpitations confusion ____________________________________

The reaction was recognized by (Please circle one):

- Yourself
- Routine test on your meter
- Someone else

Treatment for the reaction needed (Please circle all that apply):

- Juice/Food/Glucose tablets
- Help from someone else
- Injection of Glucagon
- Hospital/Ambulance

Date:____________________ Time:______________ ____ Blood Sugar Value:____________________

Symptoms felt or what did you notice? (Please circle all symptoms noticed)

sweating problems with vision other: ____________________________ **OR** NONE
shaking change in behavior ____________________________________
heart palpitations confusion ____________________________________

The reaction was recognized by (Please circle one):

- Yourself
- Routine test on your meter
- Someone else

Treatment for the reaction needed (Please circle all that apply):

- Juice/Food/Glucose tablets
- Help from someone else
- Injection of Glucagon
- Hospital/Ambulance

Date:____________________ Time:__________________ Blood Sugar Value:____________________

Symptoms felt or what did you notice? (Please circle all symptoms noticed)

sweating problems with vision other: ____________________________ **OR** NONE
shaking change in behavior ____________________________________
heart palpitations confusion ____________________________________

The reaction was recognized by (Please circle one):

- Yourself
- Routine test on your meter
- Someone else

Treatment for the reaction needed (Please circle all that apply):

- Juice/Food/Glucose tablets
- Help from someone else
- Injection of Glucagon
- Hospital/Ambulance

Date:____________________ Time:__________________ Blood Sugar Value:____________________

Symptoms felt or what did you notice? (Please circle all symptoms noticed)

sweating problems with vision other: ____________________________ **OR** NONE
shaking change in behavior ____________________________________
heart palpitations confusion ____________________________________

The reaction was recognized by (Please circle one):

- Yourself
- Routine test on your meter
- Someone else

Treatment for the reaction needed (Please circle all that apply):

- Juice/Food/Glucose tablets
- Help from someone else
- Injection of Glucagon
- Hospital/Ambulance

Clinical Islet Transplant Consortium (CITC)

Instructions for Blood Sugar Records (International)

Attached is a form for recording your blood sugars and insulin doses for four weeks. On the back of the form are spaces to record details of any low blood sugars you may have during that time.

You will be required to complete blood sugar and insulin records throughout the entire time that you remain on the research protocol. If you need additional blood sugar logs please contact us.

Use the steps below as a guideline for filling out the forms:

- During the 4-weeks prior to each of your 3-month visits, please check your blood sugar a minimum of 4 times per day.

- **One week prior to your next visit starting on date please check your blood sugar 7 times per day** (this blood sugar record is in color to help remind you of the need for more intensive recording this week.)
  - **before breakfast, lunch and dinner**
  - **2 hours after breakfast, lunch and dinner**
  - **at bedtime**

- Record your blood sugars in the appropriate spaces indicated by the times listed on the sheet.

  - If your blood sugar falls below 3.0 mmol/L or you need assistance to recover from a low blood sugar event, fill out the hypoglycemia log on the back of the page. Record any symptoms, how the low blood sugar was recognized, and what treatment was taken. Extra hypoglycemic logs are included if needed.

- Record the number of insulin units you take with each injection or meal bolus. Please note the type of insulin, abbreviate Lantus insulin as **L**, NPH insulin as **N**, Regular insulin as **R**, Humalog insulin as **H**, and Novolog insulin as **A**. If you use an insulin pump, in addition to recording the bolus dose, please record the total basal dose at the end of the row in the total insulin column.

- Record the appropriate meal code in the corresponding time space.

It is very important that these meal codes are recorded.

Meal Codes:
1: Pre-meal blood sugar
2: 2 hour post- meal blood sugar
3: Bedtime

- Please complete and return **four** weeks of the blood sugar and insulin administration logs.

Appendix 7 Blood Sugar Record/Hypoglycemia Sheet and Instructions (US)

Blood Sugar Record and HYPO Log **NAME** ________________________________ SUBJECT ID __ __ - __ __ - __ __ __

Record your blood sugar a minimum of 4 times per day and number of insulin units taken daily. Record Meal Code: 1=pre-meal, 2=2 hours post-meal, 3=bedtime

Date: Total Insulin

Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Meal Code																									

Date: Insulin

Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Meal Code																									

Date: Insulin

Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Meal Code																									

Date: Insulin

Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Meal Code																									

Date: Insulin

Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Meal Code																									

Date: Insulin

Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Meal Code																									

Date: Insulin

Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Meal Code																									

For every reading below 54 mg/dl or a hypoglycemic event requiring the assistance of another, please record details on Hypoglycemia Sheet (see reverse)

Blood Sugar Record and HYPO Log (1 WEEK PRIOR TO VISIT) NAME ___________________________________ SUBJECT ID __ __ - __ __ - __ __ __

Record your blood sugar a minimum of 7 times per day and number of insulin units taken daily. Record Activity: 1=pre-meal, 2=2 hours post-meal, 3=bedtime

Date:						Breakfast (Pre and 2 hr. post)					Lunch (Pre and 2 hr post)					Dinner (Pre and 2 hr post)					Bedtime				Total Insulin
Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Activity																									

Date:						Breakfast (Pre and 2 hr. post)					Lunch (Pre and 2 hr post)					Dinner (Pre and 2 hr post)					Bedtime				Insulin
Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Activity																									

Date:						Breakfast (Pre and 2 hr. post)					Lunch (Pre and 2 hr post)					Dinner (Pre and 2 hr post)					Bedtime				Insulin
Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Activity																									

Date:						Breakfast (Pre and 2 hr. post)					Lunch (Pre and 2 hr post)					Dinner (Pre and 2 hr post)					Bedtime				Insulin
Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Activity																									

Date:						Breakfast (Pre and 2 hr. post)					Lunch (Pre and 2 hr post)					Dinner (Pre and 2 hr post)					Bedtime				Insulin
Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Activity																									

Date:						Breakfast (Pre and 2 hr. post)					Lunch (Pre and 2 hr post)					Dinner (Pre and 2 hr post)					Bedtime				Insulin
Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Activity																									

Date:						Breakfast (Pre and 2 hr. post)					Lunch (Pre and 2 hr post)					Dinner (Pre and 2 hr post)					Bedtime				Insulin
Time	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	1200	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Activity																									

For every reading below 54 mg/dl or a hypoglycemic event requiring the assistance of another, please record details on Hypoglycemia Sheet (see reverse)

Hypoglycemia Sheet

If you need more space, please copy an extra sheet

Date:____________________ Time:__________________ Blood Sugar Value:___________________

Symptoms felt or what did you notice? (Please circle all symptoms noticed)

sweating problems with vision other: ____________________________ **OR** NONE
shaking change in behavior ___________________________________
heart palpitations confusion ___________________________________

The reaction was recognized by (Please circle one):

- Yourself
- Routine test on your meter
- Someone else

Treatment for the reaction needed (Please circle all that apply):

- Juice/Food/Glucose tablets
- Help from someone else
- Injection of Glucagon
- Hospital/Ambulance

Date:____________________ Time:______________ ____ Blood Sugar Value:___________________

Symptoms felt or what did you notice? (Please circle all symptoms noticed)

sweating problems with vision other: ____________________________ **OR** NONE
shaking change in behavior ___________________________________
heart palpitations confusion ___________________________________

The reaction was recognized by (Please circle one):

- Yourself
- Routine test on your meter
- Someone else

Treatment for the reaction needed (Please circle all that apply):

- Juice/Food/Glucose tablets
- Help from someone else
- Injection of Glucagon
- Hospital/Ambulance

Date:____________________ Time:__________________ Blood Sugar Value:___________________

Symptoms felt or what did you notice? (Please circle all symptoms noticed)

sweating problems with vision other: ____________________________ **OR** NONE
shaking change in behavior ___________________________________
heart palpitations confusion ___________________________________

The reaction was recognized by (Please circle one):

- Yourself
- Routine test on your meter
- Someone else

Treatment for the reaction needed (Please circle all that apply):

- Juice/Food/Glucose tablets
- Help from someone else
- Injection of Glucagon
- Hospital/Ambulance

Date:____________________ Time:__________________ Blood Sugar Value:___________________

Symptoms felt or what did you notice? (Please circle all symptoms noticed)

sweating problems with vision other: ____________________________ **OR** NONE
shaking change in behavior ___________________________________
heart palpitations confusion ___________________________________

The reaction was recognized by (Please circle one):

- Yourself
- Routine test on your meter
- Someone else

Treatment for the reaction needed (Please circle all that apply):

- Juice/Food/Glucose tablets
- Help from someone else
- Injection of Glucagon
- Hospital/Ambulance

Clinical Islet Transplant Consortium (CITC)

Instructions for Blood Sugar Records (US)

Attached is a form for recording your blood sugars and insulin doses for four weeks. On the back of the form are spaces to record details of any low blood sugars you may have during that time.

You will be required to complete blood sugar and insulin records throughout the entire time that you remain on the research protocol. If you need additional blood sugar logs please contact us.

Use the steps below as a guideline for filling out the forms:

- During the 4-weeks prior to each of your 3-month visits, please check your blood sugar a minimum of 4 times per day.

- **One week prior to your next visit starting on date please check your blood sugar 7 times per day** (this blood sugar record is in color to help remind you of the need for more intensive recording this week.)
  - **before breakfast, lunch and dinner**
  - **2 hours after breakfast, lunch and dinner**
  - **at bedtime**

- Record your blood sugars in the appropriate spaces indicated by the times listed on the sheet.

  - If your blood sugar falls below 54mg/dL or you need assistance to recover from a low blood sugar event, fill out the hypoglycemia log on the back of the page. Record any symptoms, how the low blood sugar was recognized, and what treatment was taken. Extra hypoglycemic logs are included if needed.

- Record the number of insulin units you take with each injection or meal bolus. Please note the type of insulin, abbreviate Lantus insulin as **L**, NPH insulin as **N**, Regular insulin as **R**, Humalog insulin as **H**, and Novolog insulin as **A**. If you use an insulin pump, in addition to recording the bolus doses, please record the total basal dose at the end of the row in the total insulin column.

- Record the appropriate meal code in the corresponding time space.

It is very important that these meal codes are recorded.

Meal Codes:
1: Pre-meal blood sugar
2: 2 hour post- meal blood sugar
3: Bedtime

- Please complete and return **four** weeks of the blood sugar and insulin administration logs.

Appendix 8 HYPO Symptom Key

If the subject selected this symptom on the HYPO log….	Answer question B1 on the Blood Sugar Record and HYPO Events eCRF……	If the subject wrote this in the "Other" section……	Answer question B1 on the Blood Sugar Record and HYPO Events eCRF……
• Problems with vision	**Visual (B)**	• Eyes will not focus • Impaired vision • Diplopia	**Visual (B)**
• Change in behavior	**Behavioral (C)**	• Unable to sleep • Irritable • Stressed out • Nervous • "Wanting to sit down and do nothing"	**Behavioral (C)**
• Sweating • Shaking • Heart palpitations	**Autonomic (A)**	• Light-headed • Dizzy • Weakness • Tired • Headache • Sleepy • Difficulty walking or talking • Slow responses • Delayed motor skills • Loss of balance	**Other neuro (D)**
• Confusion	**Confusion (E)**	• Inability to perform simple math • "Out of it" •	**Confusion (E)**
•		• Seizures	**Seizures (F)**
• None	**None (G)**	• None	**None (G)**

Appendix 9 Full HYPO Score Source Document

Subject ID __ __ - __ __ - __ __ __ **Date __ __ / __ __ __ / __ __ __ __**
(dd/mmm/yyyy)

Full HYPO Score Source Document

Questions for Calculation of Full HYPO Score
(Visits 03 [q6mo] and 365 days post-initial transplant)

The subject should give his/her best estimate to answer each of the following questions, without reference to previously completed HYPO source documents.

1. How many hypoglycemic episodes in the past year have you needed help to recognize?

_____

2. How many hypoglycemic episodes in the past year have you needed help to treat?

_____

3. How many hypoglycemic episodes in the past year have you treated with glucagon?

_____

4. How many hypoglycemic episodes in the past year have required an ambulance call?

_____

Appendix 10 Accountability Log for Glucometers

GLUCOMETER ACCOUNTABILITY LOG STUDY MATERIALS BINDER

Name of Institution	**IND#: 9336**
Protocol Title: **Islet Transplantation in Type 1 Diabetes**	
Site Principal Investigator:	

Date	Number Received	Number Dispensed	Site Total	Assigned Subject	Serial Number	Date Assigned	Date Subject Returned	Reason Returned	Date Returned to Fisher

Page ___ of ___

Appendix 11 Accountability Log for CGMS®

CGMS ACCOUNTABILITY LOG
STUDY MATERIALS BINDER

Name of Institution	**IND#: 9336**
Protocol Title: **Islet Transplantation in Type 1 Diabetes**	
Site Principal Investigator:	

Date	Number Received	Number Dispensed	Site Total	Assigned Subject	Serial Number	Date Assigned	Date Subject Returned	Reason Returned	Date Returned to Fisher

Page ___ of ___

Appendix 12 Manual Serious Adverse Event Report Form

CIT-06 ADVERSE EVENT

Page 1 of 5

Subject ID ___ ___ -___ ___ - ___ ___ ___

Report Number _____

A. ADVERSE EVENT

1. Date of adverse event _____ *(dd/mmm/yyyy)*
2. Date site became aware of AE _____ *(dd/mmm/yyyy)*
3. Adverse Event Term
4. Describe event or problem. (Include any details relating to diagnosis.)

No Yes

5. ○ ○ Is this an exacerbation of a pre-existing condition (existing prior to enrollment)?
6. Describe relevant tests/laboratory data, including dates.
7. Describe other relevant history, including preexisting medical conditions. (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

CLINICAL ISLET TRANSPLANTATION CONSORTIUM
ISLET TRANSPLANTATION IN TYPE 1 DIABETES

Version 5.0
03/Sep/2009

CIT-06 ADVERSE EVENT

Page 2 of 5

Subject ID ___ ___ -___ ___ - ___ ___ ___

Report Number _____

8. Outcomes attributed to adverse event (Check all that apply)
(ALL choices below represent an SAE except "None of the above")

☐ Death: ___/___/___ *(dd/mmm/yyyy)*

☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Disability
☐ Congenital anomaly
☐ Required intervention to prevent permanent impairment/damage
☐ Important medical event as determined by the site PI or designee
☐ None of the above (non-serious AE)

If outcome changes to an SAE during a postcomplete change, Q8a and 8b pop-up.

8a. Date the Adverse Event became a Serious Adverse Event:
___/___/___ (dd/mmm/yyyy)

8b. Date the site became aware that the Adverse Event became a Serious Adverse Event:
___/___/___ (dd/mmm/yyyy)

9. Intensity - Please follow the guidelines in the "TCAE in Trials of Adult Pancreatic Islet Transplantation"
(Select one)
○ Mild/Grade I
○ Moderate/Grade II
○ Severe/Grade III
○ Life-threatening/Grade IV
○ Death/Grade V
(If question 9 is Death/Grade V, then go to question 10)

10. Was/will an autopsy be performed? **(Select one)**
○ No
○ Yes ——— Please provide a de-identified copy to the DCC
○ Unknown

11. Indicate outcome of the event
○ Continuing
○ Resolved (or resolved with sequelae)-If resolved, give date of resolution ___/___/___ *(dd/mmm/yyyy)*

CLINICAL ISLET TRANSPLANTATION CONSORTIUM
ISLET TRANSPLANTATION IN TYPE 1 DIABETES

Version 5.0
03/Sep/2009

CIT-06 ADVERSE EVENT

Subject ID ___ ___ -___ ___ - ___ ___ ___

Page 3 of 5

Report Number _____

	No	Yes	
12.	○	○	Was a study-related islet transplant procedure ever initiated for this subject?

a. Relationship to islet transplantation
- ○ Definite
- ○ Probable
- ○ Possible
- ○ Unlikely
- ○ Unrelated, Explain: [ ]

b. Action taken regarding islet transplantation
- ○ Infusion not started
- ○ None
- ○ Interrupted but completed
- ○ Prematurely terminated

	No	Yes	
13.	○	○	Has the subject ever received immunosuppression and/or infection prophylaxis?

a. Relationship to immunosuppression/infection prophylaxis
- ○ Definite
- ○ Probable
- ○ Possible
- ○ Unlikely
- ○ Unrelated, Explain: [ ]

b. Action taken regarding immunosuppression/infection prophylaxis
- ○ None
- ○ Dose reduced
- ○ Interrupted
- ○ Discontinued
- ○ Dose increased

	No	Yes	
14.	○	○	Was the subject ever receiving intensive insulin therapy (IIT) at the time of the adverse event?

a. Relationship to intensive insulin therapy
- ○ Definite
- ○ Probable
- ○ Possible
- ○ Unlikely
- ○ Unrelated, Explain: [ ]

b. Action taken regarding intensive insulin therapy
- ○ None
- ○ Dose reduced
- ○ Interrupted
- ○ Discontinued
- ○ Dose increased

CLINICAL ISLET TRANSPLANTATION CONSORTIUM
ISLET TRANSPLANTATION IN TYPE 1 DIABETES

Version 5.0
03/Sep/2009

CIT-06

ADVERSE EVENT

Subject ID ___ ___ -___ ___ - ___ ___ ___

Report Number _____

B. SUSPECT MEDICATION(S)

	Suspect Medication 1	Suspect Medication 2	Suspect Medication 3
1. Name	i. Islet Transplantation ☐ Islet Product (check if ever recieved islets) ☐ Transplant Procedure (check if ever had transplant procedure initiated)	ii. Immunosuppression and infection prophylaxis	iii. Intensive Insulin Therapy
2. Dose	i.		ii. Units/day
3. Therapy dates (if unknown, give best estimate)	i. Date of most recent islettransplantation *(dd/mmm/yyyy)*		ii. Introduction Date __/___/____ iii. Date of last dose __/___/____ *(dd/mmm/yyyy)*
4. Diagnosis for use	Type I Diabetes Mellitus	Immunosuppression	Type I Diabetes Mellitus
5. Event abated after use stopped or dose reduced?	i. ○ No ○ Yes ○ Doesn't apply	ii. ○ No ○ Yes ○ Doesn't apply	
6.Event reappeared after reintroduction?	i. ○ No ○ Yes ○ Doesn't apply	ii. ○ No ○ Yes ○ Doesn't apply	
7. Lot number	i.		
8. Expiration Date	N/A		

CIT-06 ADVERSE EVENT

Page 5 of 5

Subject ID ___ ___ -___ ___ - ___ ___ ___

Report Number _____

C. OTHER MEDICATIONS

What concomitant medications was the subject receiving at the time of the event?
(Exclude treatment of event)

INSTRUCTIONS:

1. Select the buttons below to add data to the Other Medications text box.

   ○ Select to add data that has been entered into the subject's Concomitant Meds eCRF

   ○ Select to add data that has been entered into the subject's Study Treatment Regimen eCRF

2. Please review added data carefully for accuracy and modify this form and the Concomitant Meds eCRF and/or the Study Treatment Regimen eCRF as needed.

3. If the subject was on **insulin therapy at the time of the event**, their insulin therapy must be **added to the text box below**.

4. Add any additional medication information, if applicable.

CLINICAL ISLET TRANSPLANTATION CONSORTIUM
ISLET TRANSPLANTATION IN TYPE 1 DIABETES

Version 5.0
03/Sep/2009

Appendix 13 CIT-06 Islet After Kidney Screening Log

Site: **Coordinator:**	**Start Date:** **End Date:**	
Criterion/Reason for Ineligibility	**Tally of Subjects Who Do Not Meet this Criterion**	**Write in values that made subjects ineligible (*i.e.*, BMI, Immunosuppression regimen, insulin requirement, PRA, time to transplant)**
Calcineurin inhibitor based maintenance immunosuppression other than the following: • Tacrolimus alone • Tacrolimus in conjunction with o sirolimus, o mycophenolate mofetil, o myfortic, or o azathioprine • Cyclosporine in conjunction with o sirolimus, o mycophenolate mofetil, or o myfortic		
Unstable renal function (as per protocol)		
BMI >30 kg/m^2 or subject weight ≥90 kg		
Insulin requirement > 1.0 IU/kg/day or <15 U		
Other non-kidney organ transplant (excluding prior failed pancreas transplants as per protocol)		
Proteinuria (ACr > 300mg/g) of new onset since kidney transplantation.		
Calculated panel-reactive anti-HLA antibodies > 50%.		
Antibodies to the renal donor (*i.e.* presumed denovo).		

Appendix 14 CIT-06 Islet after Kidney Inclusion/Exclusion Criteria Checklist

The grayed-out criteria listed below require additional source documentation.

INCLUSION CRITERIA		
Criterion Met?	**Criterion**	**Location in source documents**
No ☐ Yes ☐	Male and female subjects age 18 to 68 years.	Medical record
No ☐ Yes ☐	Subjects who are able to provide written informed consent and to comply with the procedures of the study protocol.	
No ☐ Yes ☐	Subjects in the United States must have one of the following payment mechanisms in place: a. Medicare, b. A third-party insurer who agrees, via pre-authorization, to pay for participation in the study, or c. Another mechanism of payment (self-pay, hospital, university, donations, etc.) for participation in the study.	
No ☐ Yes ☐	Clinical history compatible with T1D with disease onset < 40 years of age and insulin-dependence for ≥ 5 years at the time of enrollment, and a sum of subject age and insulin dependent diabetes duration of ≥28.	Endocrinologist questionnaire
No ☐ Yes ☐	Absent stimulated c-peptide (< 0.3 ng/mL) in response to a MMTT (Boost® 6 mL/kg BW to a maximum of 360 mL; another product with equivalent caloric and nutrient content may be substituted for Boost®) measured at 60 and 90 min after start of consumption.	Central lab results
No ☐ Yes ☐	Subjects who are ≥ 3 months post-renal transplant who are taking appropriate calcineurin inhibitor based maintenance immunosuppression ([tacrolimus alone or in conjunction with sirolimus, mycophenolate mofetil, myfortic, or azathioprine; or cyclosporine in conjunction with sirolimus, mycophenolate mofetil, or myfortic] ± Prednisone ≤ 10 mg/day).	Medical record
No ☐ Yes ☐	Stable renal function as defined as creatinine of no more than one third greater than the average creatinine determination performed in the 3 previous months prior to islet transplantation, until rejection, obstruction or infection is ruled out.	Local lab results

INCLUSION CRITERIA		
Criterion Met?	**Criterion**	**Location in source documents**
No ☐ Yes ☐ (Circle eligible option)	Reduced awareness of hypoglycemia manifested by a Clarke score of 4 or more measured upon study enrollment and at least one episode of severe hypoglycemia in the 12 months prior to study enrollment. This criterion requires that there has been involvement in intensive diabetes management. Such management must be under the direction of an endocrinologist, diabetologist, or diabetes specialist with at least 3 clinical evaluations during the 12 months prior to study enrollment; OR After enrollment followed by at least 4 months of IIT, a subject must have a reduced awareness of hypoglycemia manifested by a Clarke score of 4 or more and at least 1 episode of **severe hypoglycemia**; OR Any subject not meeting the hypoglycemia option must receive intensive insulin therapy (IIT) for a minimum of 12 months under the care of an experienced diabetes specialist. At the end of this period s/he must have both an HbA1c $\geq$ 7.5% and a value for HbA1c within the 95% confidence interval for the HbA1c in the preceding month of IIT. If the HbA1c has fallen below this 95% confidence interval, the subject must be followed for at least one more month of IIT to achieve a stable HbA1c above 7.5%, as per the above definition; OR Any subject not meeting one of the above options in this criterion may continue IIT beyond the required 12 months. The subject will be eligible for islet transplantation if the second or third option is met after 12 months of IIT.	Endocrinologist questionnaire Screenshot of Clarke score Blood Sugar Record Central lab results

EXCLUSION		
Criterion Met?	**Criterion**	**Location in source documents**
No ☐ Yes ☐	Weight more than 90 kg or BMI > 30 kg/m^2.	Medical record
No ☐ Yes ☐	Insulin requirement of >1.0 IU/kg/day or <15 U/day.	Medical record
No ☐ Yes ☐	Other (non-kidney) organ transplants except prior failed pancreatic graft where graft failure is attributed to thrombosis within the first 4 weeks or to other technical reasons that require graft pancreatectomy; with the graft pancreatectomy occurring more than 6 months prior to enrollment.	Medical record
No ☐ Yes ☐	Untreated or unstable proliferative diabetic retinopathy.	CIT06 Retinopathy source document
No ☐ Yes ☐	Blood Pressure: SBP > 160 mmHg or DBP >100 mmHg despite treatment with antihypertensive agents.	Medical record
No ☐ Yes ☐	Calculated GFR of ≤ 40 mL/min/1.73 m^2 using the subject's measured serum creatinine and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [1]. Strict vegetarians (vegans) will be excluded only if their estimated GFR is ≤35 mL/min/1.73 m^2.	Screen shot of CIT06 General Assessment eCRF, section F, GFR
No ☐ Yes ☐	Proteinuria (albumin/creatinine ratio or ACr > 300mg/g) of new onset since kidney transplantation.	Medical record
No ☐ Yes ☐	Calculated panel-reactive anti-HLA antibodies > 50%. Subjects with calculated anti-HLA antibodies ≤ 50% will be excluded if any of the following are detected: • Positive cross-match, • Islet donor-directed anti-HLA antibodies detected by Luminex Single Antigen/specificity bead including weakly reactive antibodies that would not be detected by a a flow cross-match is compatible, or • Antibodies to the renal donor (*i.e.* presumed denovo).	Central lab results

EXCLUSION		
Criterion Met?	**Criterion**	**Location in source documents**
No ☐ Yes ☐	For female subjects: Positive pregnancy test, presently breast-feeding, or unwillingness to use effective contraceptive measures for the duration of the study and 4 months after discontinuation. For male subjects: intent to procreate during the duration of the study or within 4 months after discontinuation or unwillingness to use effective measures of contraception. Oral contraceptives, Norplant®, Depo-Provera®, and barrier devices with spermicide are acceptable contraceptive methods; condoms used alone are not acceptable.	
No ☐ Yes ☐	Presence or history of active infection including hepatitis B, hepatitis C, HIV, or tuberculosis (TB). Subjects with laboratory evidence of active infection are excluded even in the absence of clinical evidence of active infection	Medical record
No ☐ Yes ☐	Negative screen for EBV by IgG determination at time of screening or previous kidney transplant.	Medical record
No ☐ Yes ☐	Invasive aspergillus, histoplasmosis, and coccidoidomycosis infection within one year prior to study enrollment.	
No ☐ Yes ☐	Any history of malignancy except for completely resected squamous or basal cell carcinoma of the skin.	
No ☐ Yes ☐	Known active alcohol or substance abuse.	
No ☐ Yes ☐	Evidence of Factor V Leiden mutation.	
No ☐ Yes ☐	Any coagulopathy or medical condition requiring long-term anticoagulant therapy (*e.g.* warfarin) after islet transplantation (low-dose aspirin treatment is allowed) or subjects with INR > 1.5. The use of Plavix is allowed only in conjunction with mini-laparotomy procedure at the time of islet transplant.	

EXCLUSION		
Criterion Met?	**Criterion**	**Location in source documents**
No ☐ Yes ☐	Severe co-existing cardiac disease, characterized by any one of these conditions: • Recent MI (within past 6 months); • Evidence of ischemia on functional cardiac exam within the last year; • Left ventricular ejection fraction < 30%; or • Valvular disease requiring replacement with prosthetic valve.	Medical record
No ☐ Yes ☐	Persistant elevation of liver function tests at the time of study entry. Persistent SGOT (AST), SGPT (ALT), alkaline phosphatase or total bilirubin, with values > 1.5 times normal upper limits will exclude a subject.	Medical record
No ☐ Yes ☐	Active infections (except mild skin and nail fungal infections).	
No ☐ Yes ☐	Acute or chronic pancreatitis.	
No ☐ Yes ☐	Active peptic ulcer disease, symptomatic gallstones, or portal hypertension.	
No ☐ Yes ☐	Treatment with any anti-diabetic medication other than insulin within 4 weeks of enrollment.	
No ☐ Yes ☐	Use of any investigational agents within 4 weeks of enrollment.	
No ☐ Yes ☐	Administration of live attenuated vaccine(s) within 2 months of enrollment.	
No ☐ Yes ☐	Any medical condition that, in the opinion of the investigator, will interfere with the safe participation of the trial. (Cancer screenings should be performed per current American Cancer Society guidelines).	
No ☐ Yes ☐	Any condition other than T1D as the primary cause of end stage renal disease (ESRD) in the native kidney.	
No ☐ Yes ☐	Positive screen for BK virus by PCR determination at time of screening.	
No ☐ Yes ☐	A previous islet transplant.	

EXCLUSION		
Criterion Met?	**Criterion**	**Location in source documents**
No ☐ Yes ☐	A kidney transplant subject with type 1 diabetes who has an HbA1c < 7.5 and no hx of severe hypoglycemia.	

I have reviewed this checklist and confirm that all inclusion/exclusion criteria have been met.

_____ _____

Signature of PI or designee (listed on 1572) Date

Appendix 15 CIT-06 Guide to Deviation Classifications

Major Deviations: Complete the Protocol Deviation eCRF immediately. It is also recommended that you notify the DCC Protocol Coordinator too.

Please note that informed consent documentation, eligibility documentation, and documentation to assess the primary endpoint must be available at the time of the monitoring visit. If not, they will be considered a major deviation, regardless of whether documentation is found after the conclusion of the visit.

Minor deviations: Complete the Protocol Deviation eCRF within a reasonable time frame.

Category	Major Deviations	Minor Deviations
Informed Consent	➢ Consent not signed ➢ Wrong version of enrollment or randomization consent; i.e., does not match version of protocol, not IRB or NIH approved ➢ Consent not signed at appropriate time. e.g. enrollment consent must be signed before screening and randomization consent immediately after randomization ➢ Investigator did not document his/her explanation or involvement of the informed consent process in the medical record ➢ Documentation of informed consent in medical record is not available during monitoring visit	➢ Consent documentation in medical record was not entered on the day of informed consent ➢ X's entered instead of initials on IC source documents or in future testing portion of consent forms
Screening and Eligibility **See table on Page 3**	➢ Eligibility information is measurable and verifiable, but documentation does not exist or is not available at time of monitoring visit ➢ PRA exclusion, refer to MOP	➢ Non-metabolic screening assessment windows exceeded ➢ PPD Skin test missing or out of window for SC visit only (*still needed for eligibility at WL/BL; see page 4*) ➢ HTLV screening serology not done

Category	Major Deviations	Minor Deviations
Study Medications	➢ Infusion of study drug (immunosuppression, induction) not completed within designated hours of reconstitution ➢ Infusion not completed before islet transplantation ➢ Study drugs (including induction medications and maintenance immunosuppressants) not administered per protocol (*see exception for sirolimus, in minor deviation column*) ➢ Drug provided for one CIT study used in the wrong study ➢ Etanercept dosing not administered per protocol	➢ Pre-medication not administered as described per protocol ➢ Post-initial, pre-trough CIT07 sirolimus dose not administered per protocol prior to Version 5.0
Concomitant/Prophylactic Medications	➢ NO prophylactic meds (also considered study drugs) administered—and no clinical rationale documented	➢ Dosing of prophylactic medications not according to protocol (*Doses adjusted due to a clinical rationale do not constitute a deviation*) ➢ NO prophylactic meds (also considered study drugs) administered—with clinical rationale documented
Prohibited Medications (See Section 5.5)	➢ Medications prohibited in protocol administered to subject	

Category	Major Deviations	Minor Deviations
Endpoint & Metabolic Assessments	➢ Hypo events/ blood sugar records inadequate for calculation of eligibility or primary endpoint or not available at time of monitoring visit ➢ Post-transplant metabolic assessments missing or out of window o Not executing FSIGT/MMT properly at 75 or 365 days after initial and final transplant (i.e., incorrect insulin/glucose dosing) o MMTT done, but 60- or 90-min sample ≥ 15 min outside of timepoints ➢ Critical post-transplant visits out of window: e.g. Day 75 and 1 year after initial and final transplant	➢ Hypo events/blood sugar records incomplete and inadequate for calculation of secondary endpoints ➢ Blood sugar records incomplete, but enough data available for calculation of primary endpoint ➢ Only one post-prandial C-peptide collected on Day 3 or Day 7 ➢ FSIGT done but some samples missed or drawn at wrong timepoint ➢ MMTT done, but 60- or 90-min sample drawn up to 15 min outside of timepoints
Adverse Event Reporting	➢ Insufficient AE collection: Grade 3 and higher not reported ➢ Failure to report SAE within 24 hours	➢ Grade 1 and 2 AEs not entered into eCRF, though documented in patient record
Clinical Labs & Assessments	➢ Labs affecting safety endpoints not completed ➢ Physical exam not done at any post-transplant visit where it is required ➢ No b cells collected for crossmatch	➢ Chemistries, lipids, LFTs, sodium, etc, missed or out of window ➢ CMV by PCR missed Day 180 ➢ Non-critical visits out of window ➢ Physical not countersigned by someone on 1572 ➢ Vitals missed at visits when H&P is due ➢ Weight missed on visits when H&P due ➢ Annual PPD skin test not done
Mechanistic or Archived Sample Collection	➢ Samples drawn without subject consent	➢ Samples not drawn due to blood volume issues. (Samples not drawn due to lack of consent do not constitute a deviation.)

Assessment	Deviation impact if a subject is placed on the wait list (assessments from Visit 01 - SC)		Deviation impact if a subject is randomized (assessments from Visit 03-04—WL/BL)	
	Not Done	Out of Window	Not Done	Out of Window◆
General Assessments				
Medical and diabetes history	Major			
Eligibility letter	Major			
Mammogram (V3.0 & CIT04 sites)	Minor	Minor		Minor◆
Retinopathy exam (screening)	Major	Major		Minor◆
Retinal photos* (WL/BL)			Minor	Minor◆
Physical exam	Minor	Minor		Major
Vitals	Major	Major		Minor◆
QOL			Minor	Minor◆
Chest x-ray	Major	Major		Minor◆
Abdominal US	Major	Major		Minor◆
ECG	Major	Major		Minor◆
Cardiac Stress Test/Angiogram	Major	Minor		
PPD	Major	Major		Major
Local Lab Assessments				
CBC	Major	Major		Minor◆
Chemistry	Minor	Minor		Minor◆
Lipids	Major		Major	Minor◆
Thyroid function	Minor	Minor		Minor◆
Pregnancy test	Major		Major	Major
PSA	Major	Minor		Minor◆
Serology	Major**	Major**	Major**	Major**
EBV IgG	Major			
CMV IgG/IgM			Major	Major (-) N/A (+)
CMV/EBV by PCR			Major	
Coagulation	Major	Minor	Major	Minor◆
Blood type	Major			
HLA	Major			
Crossmatch			Major	Minor◆
Central Lab/Metabolic Assmts				
First morning spot urine	Major		Major	
GFR	Major		Major	Minor◆
HbA1c	Major			Minor◆
Fasting serum glucose/c-pep.	Minor		Minor	
MMT	Major			
FSIGT*			Minor	Minor
Local Metabolic Assmts				
CGMS			Minor	Minor
BSR source docs/calculations	Major		Minor	Minor◆
Calculated Metabolic Assmts				
Clarke survey	Major		Minor	Minor◆
Mechanistic Assays				
PRA/Alloantibody	Major		Major	Major
Autoantibody			Minor	
TAT/C3a/c-peptide			Major	
Archived samples	Minor			

◆Minor deviations in this column only apply if the assessment has not been repeated within the required window one time only. Otherwise, the participant should not be randomized until the assessment can be collected.

*Does not constitute a deviation if conducted while subject is on waitlist.

Assessment	Deviation impact at Day 75		Deviation impact at Day 365	
	Not Done	Out of Window	Not Done	Out of Window
General Assessments				
Retinopathy exam			Minor	Minor
Retinal photos			Minor*	Minor*
Physical exam	Major	Major	Major	Major
Vitals	Minor	Minor	Minor	Minor
QOL	Major	Major	Minor	Minor
Chest x-ray			Minor	Minor
Abdominal US			Minor	Minor
ECG			Minor	Minor
PPD			Minor	Minor
Local Lab Assessments				
CBC	Minor	Minor	Minor	Minor
Chemistry	Minor	Minor	Minor	Minor
Lipids	Minor	Minor	Minor	Minor
Serology			Minor	Minor
CMV IgG/IgM			Minor	Minor
CMV by PCR	Minor	Minor		
Central Lab/Metabolic Assmts				
First morning spot urine	Major	Major	Major	Major
GFR	Major	Major	Major	Major
HbA1c	Major	Major	Major	Major
Fasting serum glucose/c-pep.	Major	Major	Major	Major
MMT	Major	Major	Major	Major
FSIGT	Minor	Minor	Minor	Minor
Local Metabolic Assmts				
CGMS	Minor	Minor	Minor	Minor
BSR source docs/calculations	Major	Minor	Major	Minor
Calculated Metabolic Assmts				
Clarke survey			Major	Minor
Mechanistic Assays				
PRA/Alloantibody	Major	Major	Major	Major
Autoantibody	Minor	Minor	Minor	Minor
Archived samples	Minor	Minor	Minor	Minor

*Only if the assessment was collected at baseline. If the assessment was not collected at baseline, then per protocol the assessment shouldn't be collected at this time point.

Appendix 16 Hypoglycemic Events Assessment Source Document

Hypoglycemic Events Assessment

Subject ID_____

Visit Number_____

Visit Date_____

Has the subject experienced any hypoglycemic events (blood glucose <54 mg/dL [3.0 mmol/L] since the last visit?

- o **NO**
- o **YES - ALL hypoglycemic events must be documented on the HYPO log source documents and entered into the Blood Sugar Record and Hypoglycemic Events eCRF.**

_____ _____

Coordinator Signature *Date*

Appendix 17 Source Tool: Eligibility for Second Transplant CIT06 Protocol Version 4.0

1. Does the subject have partial graft function (confirmed by local c-peptide if the subject is between days 30-74 post-first islet infusion, or by both central MMTT and local c-peptide if the subject is beyond day 75)?
   ( )Yes ( )No ( )N/A *If 'No', complete prior to assessing eligibility for a second transplant.*

2. If the subject has graft failure, have the graft failure assessments been completed?
   ( )Yes ( )No ( )N/A *If 'No', complete prior to assessing eligibility for a second transplant.*

3. Is the subject between 30 days and 8 months post-first islet infusion?
   ( )Yes ( )No *If 'No', subject is not eligible for a second transplant. Continue study follow-up.*

4. Has the subject confirmed that they want to receive another transplant?
   ( )Yes ( )No *Please document this conversation in the chart.*

5. Is all subject data up-to-date in the electronic study database?
   ( )Yes ( )No *If no, please complete outstanding data entry.*

Source documentation must be available to support the following eligibility criteria:

Y/N	Criterion	Notes
	1. Subject received ≥5,000 IEQ/kg with the first transplant, but failed to achieve or maintain insulin independence	
	2. Subject has been compliant with study monitoring and prescribed immunosuppressive therapy.	
	3. No evidence of a serious and life-threatening infection, AE, or other condition that precludes attempting an intraportal injection or continuation of the post-transplant treatment regimen.	
	4. Subject has no unresolved SAEs.	
	5. No evidence of PTLD, requiring complete withdrawal from immunosuppressive therapy.	
	6. No evidence of hypersensitization, allergic responses, or other potentially serious drug reactions to medications required by the protocol.	
	7. Stable renal function as defined as being a creatinine of no more than one third greater than the average creatinine determination performed in the 3 previous months, until rejection, obstruction or infection is ruled out.	
	8. Any medical condition that, in the opinion of the investigator, will interfere with a safe and successful second islet transplant.	

Completed by: _____ date: _____

Investigator Signature: _____date:_____

Appendix 18 Source Tool: Eligibility for Third Transplant CIT06 Protocol Version 4.0

1. Does the subject have partial graft function (confirmed by local c-peptide if the subject is between days 30-74 post-second islet infusion, or by both central MMTT and local c-peptide if the subject is beyond day 75)?
   ( )Yes ( )No ( )N/A *If 'No', subject is not eligible for a third transplant.*

2. Is the subject between 30 days and 8 months post-first initial islet infusion?
   ( )Yes ( )No *If 'No', subject is not eligible for a third transplant. Continue study follow-up.*

3. Has the subject confirmed that s/he wants to receive another transplant?
   ( )Yes ( )No *Please document this conversation in the chart.*

4. Is all subject data up-to-date in the electronic study database?
   ( )Yes ( )No *If no, please complete outstanding data entry.*

Source documentation must be available to support the following eligibility criteria:

Y/N	Criterion	Notes
	1. Subject received ≥4,000 IE/kg with the second transplant, but remains dependent on insulin for longer than one month after the second transplant.	
	2. There is evidence of **partial graft function** at one month**.**	
	3. The CIT PIs, Site PIs, and the Steering Committee have determined that there are no relevant protocol deviations at the site.	
	4. The subject has been compliant with study monitoring and prescribed immunosuppressive therapy.	
	5. No evidence of a serious and life-threatening infection, AE, or other condition that precludes attempting an intraportal injection or continuation of the post-transplant treatment regimen.	
	6. Subject has no unresolved SAEs.	
	7. No evidence of PTLD, requiring complete withdrawal from immunosuppressive therapy.	
	8. No evidence of hypersensitization, allergic responses, or other potentially serious drug reactions to medications required by the protocol.	
	9. Stable renal function as defined as being a creatinine of no more than one third greater than the average creatinine determination performed in the 3 previous months, until rejection, obstruction or infection is ruled out.	

Completed by: _____ date:_____

Investigator Signature: _____date:_____

Appendix 19 CIT-06 Retinopathy Source Document

Subject ID# ☐☐-☐☐-☐☐☐ Initials:☐☐☐ Date of Exam: ☐☐/☐☐☐/☐☐☐☐

1. CORRECTED VISUAL ACUITY	OS	OD
20/		

Instructions: Please check box if condition exists.

2. LEGALLY BLIND	Yes	No
Left eye	☐	☐
Right eye	☐	☐

3. DIABETIC RETINOPATHY DISEASE SEVERITY SCALE

Disease Severity Level	Findings Observable on Dilated Ophthalmoscopy	OS	OD
No apparent retinopathy	No abnormalities	☐	☐
Mild nonproliferative diabetic retinopathy	Microaneurysms only	☐	☐
Moderate nonproliferative diabetic retinopathy	More than just microaneurysms but less than severe nonproliferative diabetic nephropathy	☐	☐
Severe nonproliferative diabetic retinopathy	Any of the following: more than 20 intraretinal hemorrhages in each of 4 quadrants; definite venous beading in 2 or more quadrants; prominent intraretinal microvascular abnormalities in 1 or more quadrants *and no* sign of proliferative retinopathy	☐	☐
Proliferative diabetic retinopathy	One or more of the following: neovascularization, vitreous/preretinal hemorrhage	☐	☐
Unknown		☐	☐

4. DIABETIC MACULAR EDEMA DISEASE SEVERITY SCALE

Disease Severity Level	Findings Observable on Dilated Ophthalmoscopy	OS	OD
Macular edema absent		☐	☐
Mild diabetic macular edema	Some retinal thickening or hard exudates in posterior pole but distant from the center of the macula	☐	☐
Moderate diabetic macular edema	Retinal thickening or hard exudates approaching the center of the macula but not involving the center	☐	☐
Severe diabetic macular edema	Retinal thickening or hard exudates involving the center of the macula	☐	☐
Unknown		☐	☐

5. OTHER OCULAR CONDITIONS

	OS		OD	
Condition	Present	Not present	Present	Not present
Cataracts	☐	☐	☐	☐
Vitreous hemorrhage	☐	☐	☐	☐
Retinal detachment	☐	☐	☐	☐
Glaucoma	☐	☐	☐	☐

Comments:

Physician Name: _____ **Phone**: _____

Signature: _____ **FAX:** _____

E-Mail: _____

Appendix 20 CIT-06 Protocol Communication Plan

TOPIC/RELATED QUESTIONS	STUDY ROLE AND CONTACT INFORMATION
• Serious Safety Concerns • Publications • Statistical Questions • Endpoint Questions • Major Protocol Deviations • Clinical Care Questions/Concerns • SAE Review and Reporting • Grantee Budgets	**Thomas L. Eggerman, MD, PhD** **Medical Monitor** Director Islet Transplantation Program DDEMD/NIDDK/NIH Division of Diabetes, Endocrinology and Metabolic Diseases National Institute of Diabetes and Digestive and Kidney Diseases 6707 Democracy Boulevard, Room 697 Bethesda, MD 20892-5460 Phone: 301-594-8813 Fax: 301-480-3503 eggermant@extra.niddk.nih.gov
• Day to Day Site Activities • Informed Consent • Protocol Deviations • Amendments to Protocol • Enrollment/Screening • Investigator Meetings/Teleconferences • Site Visit Concerns • Clinical Protocol Issues • Protocol Development / Finalization • Protocol Compliance • Data Compliance	**Neal Green, MPH** **NIDDK Project Manager** DDEMD/NIDDK/NIH Division of Diabetes, Endocrinology and Metabolic Diseases National Institute of Diabetes and Digestive and Kidney Diseases 6707 Democracy Boulevard, Rm 686A Bethesda, MD 20892-5460 Phone: 301-594-8815 Fax: 301-480-3503 E-mail: greenne@niddk.nih.gov
• eCRF / Data Entry Questions • Data Management / Query Resolution • CIT Web-site Questions and Postings • Study Material Supplies (binders, QOLs, source documents etc.) • IAK MOP questions • Scheduling of Site Monitoring Visits	**Julie Qidwai, MS, CCRC** **DCC Protocol Coordinator** University of Iowa Department of Biostatistics Clinical Trials Statistical and Data Management Center 2400 University Capital Centre Iowa City, IA 52242 Phone: 319-384-4165 Fax: 319-335-3960 E-mail: julie-qidwai@uiowa.edu **Dixie J. Ecklund, RN, MSN, MBA** **Associate Director** University of Iowa Department of Biostatistics Clinical Trials Statistical Data Management Center 2400 University Capital Centre Iowa City, IA 52242 Phone: 319-335-8446 Fax: 319-335-6535 dixie-ecklund@uiowa.edu

TOPIC/RELATED QUESTIONS	STUDY ROLE AND CONTACT INFORMATION
• Communication with Clinical Site Principal Investigators • SAE/AE notification • Statistical Questions in Parallel with NIH Medical Monitors	**Larry Hunsicker, MD** **DCC Clinical Trial Physician** University of Iowa Hospitals and Clinics Department of Internal Medicine T304 GH Iowa City, IA 52242 Phone: 319-356-4763 Fax: 319-353-4231 Lawrence-hunsicker@uiowa.edu **Bill Clarke, PhD** **DCC Statistician** University of Iowa Department of Biostatistics Clinical Trials Statistical Data Management Center 2400 University Capital Centre Iowa City, IA 52242 Phone: 319-384-5027 Fax: 319-335-6535 William-clarke@uiowa.edumailto:
• Manufacturing • Out of Specs (OOS) for Manufacturing • Regulatory • cGCP/cGMP • Drug Accountability/Reconciliation • Drug Stability Issues • Shipping of Drugs and Islets	**Julia Goldstein, MD** **Senior Regulatory Affairs Officer** DAIT/NIAID/NIH 6610 Rockledge Drive Room 3044 Bethesda, MD 20892 Phone: 301-451-3112 Fax: 301-480-1537 goldsteinj@niaid.nih.gov **Christine W. Czarniecki, PhD** **Chief, Regulatory and Industry Affairs** DAIT/NIAID/NIH 6610 Rockledge Drive Room 3059 Bethesda, MD 20892 Tel: 301-451-4407 Fax: 301-402-2571 cczarniecki@niaid.nih.gov
• Collection of Regulatory Documents	**Deb Feddersen** **DCC Regulatory Coordinator** Clinical Trials Statistical & Data Management Center University of Iowa 2400 University Capitol Centre Iowa City, IA 52242 Phone: 319.353.4240 Fax: 319.353.3960 deb-feddersen@uiowa.edu
• Laboratory Manual Questions	**Cynthia Diltz, RN, BSN, CCRC** **DCC Protocol Coordinator** Department of Biostatistics Clinical Trials Statistical & Data Management Center University of Iowa 2400 University Capitol Centre Iowa City, IA 52242 Phone : 319-353-4982 Fax : 319-353-3960 cynthia-diltz@uiowa.edu

Appendix 21 CIT-06 ADJUDICATION QUESTIONNAIRE

Site Coordinator Instructions:

At each quarterly visit subjects will be asked these questions concerning possible cardiovascular events or renal outcomes. Subjects will be instructed to think about the period of the time lapsed since their last visit approximately three months prior. A Serious Advert Event should be completed for each affirmative response and adjudication documentation according to the CIT-06 MOP must be completed and submitted to the Clinical Trial Physician at the DCC.

	No	**Yes**	
1.			Death
			a. Date of death: __ __/__ __ __/__ __ __ __ (DD/MMM/YYYY)
2.			Stroke
			a. Date of stroke: __ __/__ __ __/__ __ __ __ (DD/MMM/YYYY)
3.			Mycardial Infarction (MI)
			a. Date of MI: __ __/__ __ __/__ __ __ __ (DD/MMM/YYYY)
4.			Limb amputation above the ankle
			a. Date of amputation: __ __/__ __ __/__ __ __ __ (DD/MMM/YYYY)
5.			Renal failure
			a. Date of renal failure: __ __/__ __ __/__ __ __ __ (DD/MMM/YYYY

Appendix 22 CIT-06 Adjudication OUTCOME Documentation Form

This form is used to document key outcome information for Death and non-fatal events: Myocardial Infarction, Stroke, Renal Failure, and Limb Amputation (above the ankle only).

If more than one non-fatal event of the same type is suspected to have occurred during one hospitalization (i.e. the subject is suspected to have two strokes during one hospitalization), please complete a second OUTCOME form. Otherwise, please use this form to capture all applicable events that may have occurred during one hospitalization.

Subject ID: ___ ___/___ ___/___ ___ ___

Data Collector's Initials: ___ ___ ___ **Use a dash (-) for no middle name.**

Date of the Data Collection: ___ ___/___ ___ ___/___ ___ ___ ___
(DD/MMM/YYYY)

A. DEATH EVENT

	No	**Yes**	
1.	○	○	Is the subject's death documented on this form?

Date of Death: ___ ___/___ ___ ___/___ ___ ___ ___
(DD/MMM/YYYY)

Go to Item 19

2. Investigator's assessment of primary cause of death: **Indicate only one.**
   - ○ Due to cardiac disease
   - ○ Non-Cardiovascular - Go to Item 4
   - ○ Unknown- Go to Item 5

3. Which of the following describes the primary Atherosclerotic Coronary Heart Disease cause of death? **Indicate only one.**
   - ○ Acute Myocardial Infarction
   - ○ Sudden Death
   - ○ Cardiovascular Unwitnessed Death (not seen > 24 hours)
   - ○ Non-atherosclerotic Cardiac Disease
   - ○ Procedural (related to coronary artery procedure)
     Specify:_____

Go to Item 7

A. DEATH EVENT (*continued*)

4. Which of the following describes the primary, Non-Cardiovascular cause of death? **Indicate only one.**.

○ Infection
○ Malignancy
○ Pulmonary
○ Gastrointestinal
○ Accidental
○ Suicide
○ Diabetes
○ Renal (Specify: _____)
○ Other (Specify: _____)

	No	**Yes**	
5.	○	○	Was the subject hospitalized at the time of their death?

└──── Go to Item7

6. Source Documentation is required. Please review the Hospital/ Death Discharge Summary to be sure it provides an accurate and complete description of the subject's death. The Death/ Discharge Summary: **Indicate only one.**.

○ Gives an accurate and complete description of the subject's death and is being sent to the DCC – Go to Item 8

○ Is being sent to the DCC and, in addition, a Physician Narrative is being Completed. The Hospital Death/ Discharge Summary does not provide sufficient detail regarding the subject's death.

○ Is unavailable and cannot be obtained from the site. (Please review the next question and complete a Physician Narrative).

Physician Narrative should support the reasons for the death classification. This narrative should be complete and concise, and should contain all the relevant information of the subject's status/clinical course before their death.

Examples of what to consider when completing Physician Narrative:

- Did the death occur shortly after an important medical event? If so, did that non-fatal event contribute to, or directly cause, the subject's death?

- Was the subject expected to die? Describe the subject's condition in detail, prior to death (i.e., If the subject had been failing or had a poor prognosis prior to death, please explain).

A. DEATH EVENT (*continued*)

- If the subject had been stable or not in the hospital, support your cause of death and describe the circumstances by which the subject was found to have died.

- Key autopsy findings, if performed, when report can be obtained.

	No	Yes	
7.	○	○	Is a Physician Narrative being sent to the DCC that describes the circumstances surrounding the death and all other details that may provide support for the investigator's classification of death?

a. Specify why it is not available: _____

	Unknown	No	Yes	
8.	○	○	○	Was an autopsy performed?

Go to Item 9

Go to Item 9

Autopsy Report: **Indicate only one.**

○ Is being sent to the DCC. [Required document]

○ Is unavailable and cannot be obtained by the site. [Send Physician Narrative (as explained in Question 11) of the principal autopsy findings to the DCC]

○ Is unable to be obtained by site and the Investigator is unaware of principal autopsy findings.

9. Date of last known creatinine: ___ ___/___ ___ ___/ ___ ___ ___ ___
(DD/MMM/YYY)

10. Creatinine Value: ___ ___ ___ mg/dl (note: mg/dL= Mmol/L/ 88.4)

	Unknown	No	Yes	
11.	○	○	○	Considering the subject's condition in the days prior to death, was the death clinically expected?
12.	○	○	○	Prior to death, did the subject have a recurrence of renal failure?

Go to Item 19

Go to Item 19

A. DEATH EVENT (*continued*)

13. Date the subject was found to have renal failure:
___ ___/___ ___ ___/___ ___ ___ ___
(DD/MMM/YYYY)

	Unknown	No	Yes	
14.	○	○	○	Were complications of acute renal failure present at the time of death?
16.	○	○	○	Did subject's refusal to reinitiate dialysis contribute to death?
15.	○	○	○	Did subject die of procedural complications related to treatment of renal failure? Specify complications: _____

Go to Item 19

Go to Item 19

17. Type of renal failure procedure with which subject had complications related to death:

○ Dialysis procedure
○ Dialysis access procedure
○ Renal re-transplantation
○ Other (Specify:_____)

18. Date of Procedure: ___ ___/___ ___ ___/ ___ ___ ___ ___
(DD/MMM/YYYY)

B. OTHER CARDIOVASCULAR OUTCOMES

	No	Yes	
19.	○	○	Are there events (other than death) to be reported on this OUTCOME form?

Go to Item 22

20. Date of Hospitalization admission for the events captured below:

___ ___/___ ___ ___/___ ___ ___ ___
(DD/MMM/YYYY)

B. OTHER CARDIOVASCULAR OUTCOMES (*continued*)

Event Source Documentation

21. Source Documentation is required. Is the Hospital Discharge Summary being sent to the DCC? **Indicate only one.**

○ Hospital Discharge Summary is being sent to the DCC

○ Hospital Discharge Summary is being sent to the DCC and, in addition, a Physician Narrative is being sent in order to provide additional details of the event(s) being reported

○ Hospital Discharge Summary can not be obtained. A Physician Narrative is being sent to the DCC that outlines the following key information in the subject's hospital course:

- Dates of admission and discharge;
- all admitting and discharge diagnoses;
- full description of clinical symptoms and physical findings; and
- relevant tests that were preformed and principal findings.

[Complete 22-49 for all outcomes being reported for this hospitalization]

C. NON-FATAL MYOCARDIAL INFARCTION

	No	**Yes**	
22.	○	○	Is a Non-fatal Myocardial Infarction (MI) being documented on this form?

└──── Go to Item 36

23. Date of MI: ___ ___/___ ___ ___/___ ___ ___ ___
(DD/MMM/YYYY)

	No	**Yes**	
24.	○	○	Did this event occur within the setting of a coronary revascularization?
25.	○	○	Did the subject experience ischemic symptoms (i.e.,pain, dyspnea, pressure) at rest of accelerated ischemic symptoms, either of which lasts 10 minutes or more and is determined by the investigator to be secondary to ischemia? [Please be sure to include event source documentation as requested in Item 21]
26.	○	○	Were cardiac markers (i.e., CK, CKMB, and/or Troponin I/T) drawn in association with this event?

└── Go to Item 28

C. NON-FATAL MYOCARDIAL INFARCTION (*continued*)

	No	Yes	
27.	○	○	Are lab reports of the PEAK values of all cardiac markers (i.e., CK, CKMB, Troponin I/T) drawn being sent to the DCC? (The lab report must include ULN and be labeled with a date and time. If CK is the only marker used, please provide all CK values in order to establish serial change. If Troponin was drawn and the results are given in ranges, please be sure and provide all reference range values.) Specify why the lab report is not available:_____
28.	○	○	Was an ECG performed in association with this event? Go to Item 36
29.	○	○	In the opinion of the investigator, are there new 'ECG changes consistent with infarction' documented in association with this event? Go to Item 36

30. Date of the ECG consistent with the infarction:

___ ___/___ ___ ___/___ ___ ___ ___
(DD/MMM/YYYY)

Please complete questions 31 – 35 based on the opinion of the investigator (not using results printed on the ECGs) regarding the presence of ECG changes consistent with infarction.

	No	Yes	
31.	○	○	New significant Q-waves (or R-waves in V1-V2) in two contiguous leads in the absence of previous LVH or conduction abnormalities
32.	○	○	Evolving ST-segment to T-wave changes in two or more contiguous leads
33.	○	○	Development of new left bundle branch block
34.	○	○	ST segment elevation requiring thrombolytics or PCI

C. NON-FATAL MYOCARDIAL INFARCTION (*continued*)

	No	Yes	
35.	○	○	Other

Please describe in detail ischemic changes seen in association with this event:
_____
_____

D. NON-FATAL STROKE

	No	Yes	
36.	○	○	Is a Non-fatal Stroke being documented on this form?

Go to Item 44

37. Date of Non-fatalStroke: ___ ___/___ ___ ___/___ ___ ___ ___
(DD/MMM/YYYY)

	Unknown	No	Yes	
38.	○	○	○	Did the subject suffer neurological deficit of sudden onset (not attributed to a readily identifiable cause such as brain tumor or trauma)? [Please be sure to include event source documentation as requested above in Item 21]

Go to Item 44

Go to Item 44

39.	○	○	○	Was neurological deficit reversible within 24 hours?
40.	○	○	○	Was a Neurology consult performed in association with this event?

Go to Item 42

Go to Item 42

D. NON-FATAL STROKE (*continued*)

41. Is the Neurology Report being sent to the DCC? **Indicate only one.**

- ○ Yes, the report is being sent to the DCC
- ○ No, site is unable to obtain a copy of this report but a Physician Narrative of the principal findings is being sent to the DCC
- ○ No, site is unable to report on any findings of the Neurology consult

	Unknown	No	Yes	
42.	○	○	○	Were imaging studies performed in association with this event?

Go to Item 44

Go to Item 44

43. Is the Imaging Studies Report being sent to the DCC?

- ○ Yes, the report is being sent to the DCC
- ○ No, site is unable to obtain a copy of this report but a Physician Narrative of the principal findings is being sent to the DCC
- ○ No, site is unable to obtain a copy of this report and is unable to report any findings of the imaging studies

E. NON-FATAL RENAL FAILURE

	No	Yes	
44.	○	○	Is Non-fatal Renal Failure being documented on this form?

Go to Item 48

45. ○ ○ Has the subject received renal dialysis treatments for established ESRD while enrolled in the study?

Start date: ___ ___/___ ___ ___/___ ___ ___ ___
(DD/MMM/YYYY)

46. ○ ○ Has the subject received a repeat renal transplant while enrolled in the study?

Start date: ___ ___/___ ___ ___/___ ___ ___ ___
(DD/MMM/YYYY)

E. NON-FATAL RENAL FAILURE (*continued*)

	No	Yes	
47.	○	○	Has the subject's serum creatinine ever been ≥ 6.0 mg/dL and confirmed at least 7 but no more than 20 days later?

a. Date of initial draw: ___ ___/___ ___ ___/___ ___ ___ ___
(DD/MMM/YYYY)

b. Serum creatinine : _____ ○ (mg/dL) ○ (Mmol/L)

Go to Item 48

F. AMPUTATION

	No	Yes	
48.	○	○	Is a leg amputation above the ankle being documented on this form?

a. Date of amputation: ___ ___/___ ___ ___/___ ___ ___ ___
(DD/MMM/YYYY)

G. SIGN OFF

49. Site Investigator: *By signing this form, I attest that the information collected on this form is true and accurate:*

Print: _____

Signature: _____

Date Signed: ___ ___/___ ___ ___/___ ___ ___ ___
(DD/MMM/YYYY)