PROTOCOL CIT-01:

OPEN RANDOMIZED MULTI-CENTER STUDY TO EVALUATE SAFETY AND EFFICACY OF LOW MOLECULAR WEIGHT SULFATED DEXTRAN IN ISLET TRANSPLANTATION

MANUAL OF PROCEDURES

VERSION 7.0

NOVEMBER 2, 2010

CONFIDENTIAL

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Glossary of Terms

AE	Adverse Event
APTT	Partial Thromboplastin Time
BW	Body Weight
CIT	Clinical Islet Transplantation
CRF	Case Report Form
CRO	Clinical Research Organization
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
GCP	Good Clinical Practices
IA	Islet Alone
IAK	Islet After Kidney
ICH	International Conference on Harmonization
IoR	Investigator of Record
IRB	Institutional Review Board
LMW-DS	Low Molecular Weight Sulfated Dextran
MOP	Manual of Procedures
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIDDK	National Institute of Diabetes & Digestive & Kidney Diseases
NIH	National Institutes of Health
PC	Protocol Coordinator
PI	Principal Investigator
PRA	Panel Reactive Antibody
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Study Coordinator
T1D	Type I Diabetic

1. General

1.1. Overview

The study Manual of Procedures (MOP) is supplied to each participating site to aid in the conduct of **Protocol CIT-01: Open Randomized Multi-Center Study to Evaluate Safety and Efficacy of Low Molecular Weight Sulfated Dextran in Islet Transplantation.**

Details not outlined in the protocol are in this manual. The current version of the MOP and protocol documents are available on a web-site maintained by the Data Coordinating Center, *www.isletstudy.org*

1.2. Study Organization

1.2.1. National Institute of Health (NIH)

NIH is responsible for all scientific aspects of the study. The Institutes (NIAID and NIDDK) are accountable to higher levels of the Executive Branch, Congress and the public for the use of government funds. Please contact the NIH Project Manager for all protocol related questions. A Communication Plan is provided detailing study roles and responsibilities, as well as contact information for study staff.

1.2.2. The Data Coordinating Center (DCC)

The University of Iowa Data Coordinating Center (DCC) provides statistical leadership for the development, implementation, and analyses of clinical trials. The DCC conducts data management and clinical trial quality control, as well as supports regulatory and technical functions (i.e. CIT website) as well as adverse event (AE) reporting. Additionally, The DCC oversees clinical site monitoring and training in protocol implementation. Please reference the Communications Plan for contact information.

1.2.3. Monitoring Clinical Research Organization (CRO)

Trial Form Support (TFS) is the Monitoring Clinical Research Organization (CRO) conducts clinical site monitoring and facilitates the reporting of adverse events to the appropriate health authority. Please reference the Communication Plan for the contact information.

1.2.4. Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (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.

1.3. Regulatory Document Collection

A Regulatory Binder will be provided by the DCC. All required regulatory documents indicated on the tabs must be included in the binder and a copy will be maintained at the DCC and the Monitoring CRO. During subsequent site visits, the binder will be reviewed to ensure it is complete and any updated documents will be copied and placed in the master regulatory binder at the Monitoring CRO and a copy at the DCC.

The site will maintain, in their Regulatory Binder: originals for the Delegation of Responsibilities Log, the Monitoring Log, and any laboratory reports/values that the Site PI has signed; and copies of all Investigator of Record documents and Financial Disclosure documents.

It is the Monitoring CRO's responsibility to collect and maintain all regulatory and clinical documentation. After the Monitoring CRO reviews and approves a document, they will provide a copy to the DCC.

Documents that are in the site's native language will not require translation (except for Informed Consent Documents, see Section 1.6 for details). However, the Monitoring CRO, acting as the responsible party, will assure that all documents are current and appropriate per regulatory requirements.

It is the DCC's responsibility to provide a monthly report to the Monitoring CRO listing all of the expired and missing documentation.

Please note, the following documents must be submitted to the Monitoring CRO prior to study activation:

- Investigator of Record (IoR) Agreement
  - Include the names of principal and sub-investigators responsible for the medical management of subjects in the study, or authorized to prescribe study medications.
  - Include the location of all sites where the study will be conducted (all clinical sites where subjects will be treated and examined).
  - List only laboratories not specified as the central laboratories for the CIT-01 protocols.
- Curriculum Vitae for all investigators listed on the Investigator of Record Agreement
- Professional Licenses for personnel listed on the Investigator of Record Agreement
  - A current license should be provided for all study personnel whose title requires licensure.
  - Include a copy of the study pharmacist license.
- Ethics Training Certification
  - The NIH requires ethics training for the investigators listed on the Investigator of Record Agreement and all study personnel directly involved in the treatment or evaluation of research subjects. There are three options for staff to receive training.
    1. NIH: Protection of Human Research Subjects: http://ohsr.od.nih.gov/
    2. NCI: Human Participant Protections Education for Research: http://cme.nci.nih.gov
    3. Any course on the protection of human subjects provided by your institution. The name and a brief description of the course are needed.
- Clinical Laboratory Certification and Normal Lab Ranges
  - Provide copies of laboratory certifications/accreditations (ISO 15189)
  - Provide copies of current laboratory normal ranges. All units of measurement, laboratory name, and document date should be included.
- EC Approval Letter and EC Correspondence
  - EC approval letters must include the following:
    - Complete Protocol Title and Protocol Number
    - Protocol Version Number
    - Date of EC Approval
    - EC Chairperson or member designee signature
- EC Approved Informed Consent and Assent forms

1.4. Site Training and Monitoring

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

1.4.1 Site Initiation Visit

Once participating centers have submitted all of the necessary regulatory documents and submitted the study protocol and consent documents to the Ethics Committee (EC), the NIAID Project Manager will contact the study coordinator to schedule a site initiation visit. An agenda will be distributed to all participating individuals. The NIAID Project Manager/DCC Protocol Coordinator will conduct the

initiation visit. Additional NIH or DCC staff may be invited to attend the visit to provide ancillary training or serve as observers. In addition to a tour of the facility, site initiation will include review of:

- Investigator and Staff Qualifications and Responsibilities;
- Protocol and Study Design;
- Facility and Equipment Review;
- Required regulatory documents and filing procedures;
- Screening, enrollment, and randomization procedures;
- Electronic Case Report Form (eCRF) Completion, Data Entry System, and CIT Website;
- Documentation Procedures and Requirements (including source documentation and proper maintenance of regulatory documents);
- Investigational Product and Study Supplies Ordering and Accountability Procedures;
- Electronic Adverse and Serious Adverse Event (SAE) reporting;
- Laboratory Procedures (including specimen collection, storage, and tracking);
- Drug accountability procedures;
- Current Good Clinical Practice (GCP) Guidelines and International Conference on Harmonization (ICH) Guidelines;
- Review of study communications plan.

1.4.2 Site Activation

Before a site may begin enrolling subjects, the site must be activated by the NIAID PM. The NIAID PM will provide a Site Activation Letter to the Site PI and Study Coordinator after the following have been completed:

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

1.4.3 Interim Monitoring

Routine monitoring visits will be conducted for all CIT studies by a CRO Site Monitor. The frequency of these visits will vary depending on protocol compliance and rate of subject enrollment. The CRO Site Monitor will contact the site staff directly to schedule interim monitoring visits; however, any questions or concerns regarding the conduct of the visit should be addressed to the NIAID PM.

The purpose of the interim monitoring visits is to ensure compliance with regulatory requirements and study procedures. These activities will involve a review of clinic, laboratory and pharmacy operations. Specifically, the CRO Site Monitor will verify source documentation against data entered in the database, perform drug accountability checks; review regulatory document binders, provide additional cGCP/ICH training as necessary, and discuss pertinent study implementation issues. The Study Coordinator (SC), PI, and Pharmacist must be available to meet with the CRO Monitor during the 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 NIAID Project Manager. Once all action items from the visit have been resolved, a signed hard copy Site Interim Monitoring Post-visit Follow-up Letter will be sent to the PI and SC and request that the site place a copy into the Site Regulatory Binder.

1.4.4 Close-out Visit

The CRO Site Monitor 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, the CRO Site Monitor 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 NIAID Project Manager. Each site is responsible for notifying the EC of the completion of the study.

1.4.5 Protocol Review Teleconference Calls

The NIAID Project Manager, the DCC Protocol Coordinator, and the Monitoring CRO will conduct scheduled conference calls with the site coordinators, as needed, to facilitate communication among the sites and review study progress. Discussion may include:

- Accrual goals and enrollment procedures
- Recruitment strategies
- Data quality compliance (*i.e.*, eCRF completion)
- Study procedures/updated study information

1.5. 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 NIAID PM 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 NIAID PM is responsible for obtaining all required approval signatures prior to finalizing the protocol document. Once the document is finalized, the NIH PM labels it as Version 1.0 and distributes an electronic PDF version to all participating sites.

1.5.1 NIH Authorization to Submit to EC

Once the protocol is finalized and the informed consent document(s) have been approved by the NIAID PM, the site will receive a memo with instructions that they may proceed with submission to the EC. Only protocol documents and consent forms indicated in this authorization memo should be submitted to the 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 EC after initial submission. Please contact the NIAID PM with any questions or concerns regarding the processes outlined above.

1.6. Consent Documents

Study-specific consent document templates will be provided to all CIT sites. Site-specific language should be inserted into the template. **All consent documents must be reviewed by the NIAID Project Manager prior to submission to the local EC.**

Each site-specific informed consent form will be reviewed by NIAID for inclusion of all essential elements and compliance with ICH Guidelines. Below is a set of instructions detailing NIAID review of your site-specific consent form.

1. Prior to EC submission, please forward, by email, the informed consent documents to the NIAID Project Manager for review.
2. The NIAID Project Manager will contact you within 5 business days with any comments/suggestions or to inform you to proceed with submission.
3. Submit the consent documents to your respective EC.
4. If the EC returns comments, amend the consent forms as necessary and forward the amended version(s) to the NIAID Project Manager.
5. Repeat step 2-4 as needed.

6. Forward an electronic copy of the final version of the consent document to NIAID for inclusion in the master site file. Additionally, maintain a copy in your local site binder.

In addition to filing the EC approved consent documents in the site regulatory binder, copies of the EC approved consents and assents must be submitted to the DCC Regulatory Coordinator. The Monitoring CRO will forward all regulatory documents to the DCC, who will be maintaining the regulatory documents for this trial.

1.6.1 Subject Consent

A signed EC- and NIAID-approved informed consent document must be obtained from each subject prior to enrollment into a CIT trial. The consent process must include a summary of the study and answers to any questions raised by the potential subject. Only after the PI or delegated study staff is assured the subject and/or legal guardian understands potential risks and benefits of participation in the study should written consent be obtained and witnessed. If there are any changes to the protocol that require modifications to the consent form, each subject must sign a new version of the consent form.

The signed informed consent document should be maintained in the following locations:

- The original form is placed in the subject's research file
- Subject and/or legal guardian will receive a copy of the signed informed consent

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

1.6.2 Translated Consent

Prior to 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 form to the DCC Protocol Coordinator for back translation. The DCC Protocol Coordinator will notify the NIAID Project Manager that the site submitted the translated consent documents and the DCC will have the consent back translated using a certified translation service. The back-translated consent document will be forwarded to the NIAID Project Manager to review and verify that all elements of informed consent are addressed. All translation issues identified by the NIAID Project Manager must be addressed before EC submission. This process may take up to 2 weeks to complete.

1.7. Data Management

1.7.1 Data Quality Control

The integrity of a study is dependent upon 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. Logical "within-form" 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 and among data forms. By necessity, these checks cannot be completed at the time of data entry. Logic checks between and among forms 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 clinical center cannot change values without the approval of the DCC. Any change to a data value that occurs after the clinical center has completed a form is tracked in the data system's 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 clinical center who is responsible for the change.

1.7.2. 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 then the DCC PC will call the site to encourage them to enter the data and complete entry of the form. In the event that a form 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.

1.7.3. Missing Values and Data Anomalies

The purpose of the data validation and quality control process is to minimize missing data and data anomalies. 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).

1.8. 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, cGCP, 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-01 is provided in Appendix 14. For major or minor protocol deviations that are not specific to a subject, please send a memo via e-mail to NIH and DCC (see Appendix 18 for e-mail template).

1.8.1. Major Protocol Deviations

A major protocol deviation:

- Impacts the inclusion and/or exclusion criteria,
- Alters protocol-specified study therapy,
- Involves administration of prohibited medications,
- Impacts the ability of the sponsor to evaluate the endpoints of the study, or
- Involves consent violations.

All major protocol 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 EC according to site's institutional policy. The Sponsor (NIH) is ultimately responsible for determining whether a protocol deviation should be reported as major or minor.

1.8.2. Minor Protocol Deviations

Minor deviations are any protocol deviations that are not defined as major deviations (see Section 1.8.1

above). Examples of minor deviations 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*.

1.9. Source Documentation

Source documentation is defined as the original documents that serve as the "raw data" for a study. These may be in paper or electronic form. Source documents include patient progress notes, laboratory reports, 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

1.9.1. Demographics

Subject demographics are determined through self-report, rather than an interpretation by the study staff. It is suggested that the study staff use the source document provided in Appendix 3 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.

1.9.2. 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 4. If a subject selects four or more responses coded "R" he or she is determined to have reduced hypoglycemia awareness.

1.9.3. Blood Sugar Record/Hypoglycemia Sheets

1.9.3.1 Instructions to Subject

Study coordinators should emphasize to the subjects the importance of completing the Blood Sugar Record source documents throughout the course of the study. 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 Appendix 5). 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 document, 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 source document, 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 types of insulin if they are using an insulin pump.

Metabolic assessments such as the LI and HYPO are a part of the inclusion criteria for these studies and must be evaluated as part of the screening visit, Visit 01. After the subject is enrolled, the study coordinator will send the study subject home with the Blood Sugar Record and Hypoglycemia Sheet source documents. The subject will fully complete these documents for 4 weeks before his/her screening eligibility can be determined. Other local laboratory screening assessments can, of course, be completed during this 1-month interval.

Additionally, it may be helpful for study coordinators 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 on Tuesday.

Entering blood sugar data into the CIT database will require that the coordinator has reconciled the subject's original source document recordings, actual insulin requirements, and glucometer download data. The data entered on the eCRFs must exactly match the subject's source documents; therefore, any changes made to the source documents, as a result of subject discussions with the study staff, must be initialed and dated by the subject and the study coordinator. If a subject records a hypoglycemic event, the coordinator should request that the subject attempt to recall any symptoms associated with the hypoglycemic event and record the results on a HYPO log.

1.9.3.2 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 6) 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 6). 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 (the subject marks "none" for symptoms experienced), even if some neuroglycopenic symptoms were also present. Conversely, hypoglycemic events that are picked up only by meter tests should not be recorded as "needing outside help".

At the following visits ,screening, every 12 months on waitlist, day 75 (after first transplant) and month 12 (after first and subsequent 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 7.

1.9.4. Quality of Life (QOL) Questionnaires (SF36 and DTSQ)

The CIT-01 study requires administration of two (2) QOL questionnaires: the SF-36 Health Survey (SF-36) and the Diabetes Treatment Satisfaction Questionnaire (DTSQ) status(s) and change (c) are self-report forms and will be provided to the subject with instructions on completing the forms. Please refer to the SOE protocol for details regarding the specific time-points when the subjects must complete the QOL questionnaires. The instructions below apply to all time-points indicated in the SOE, including the questionnaires completed while the subject is on the waiting list.

The SF36 and DTSQ forms will be completed by the individual patient. In order to assure confidentiality, the questionnaires are printed on two part paper. The study coordinator will label a set of questionnaires with the subject's ID number and the appropriate date, and then give them to the subject to complete. This process should occur in a place where the subject can be confident that s/he has privacy.

The QOL questionnaire 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 the envelopes after completing them (see below), it is important to place a single extra barcode label (taped into the top of t he 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.

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 subject's identification number;
3. Place the second copy (yellow portion) into a designated brown envelope that has been labeled with the subject's identification number;
4. Seal both envelopes and return both to the study coordinator.

The study coordinators will Federal Express the white envelope to the DCC, where the data from the questionnaires will be entered into the database by the DCC data entry staff. . The study coordinator may batch a group of subjects' white envelopes and ship these 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 but will be stored in the patients 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 # 2729-9789-6, Reference number 500008533.**

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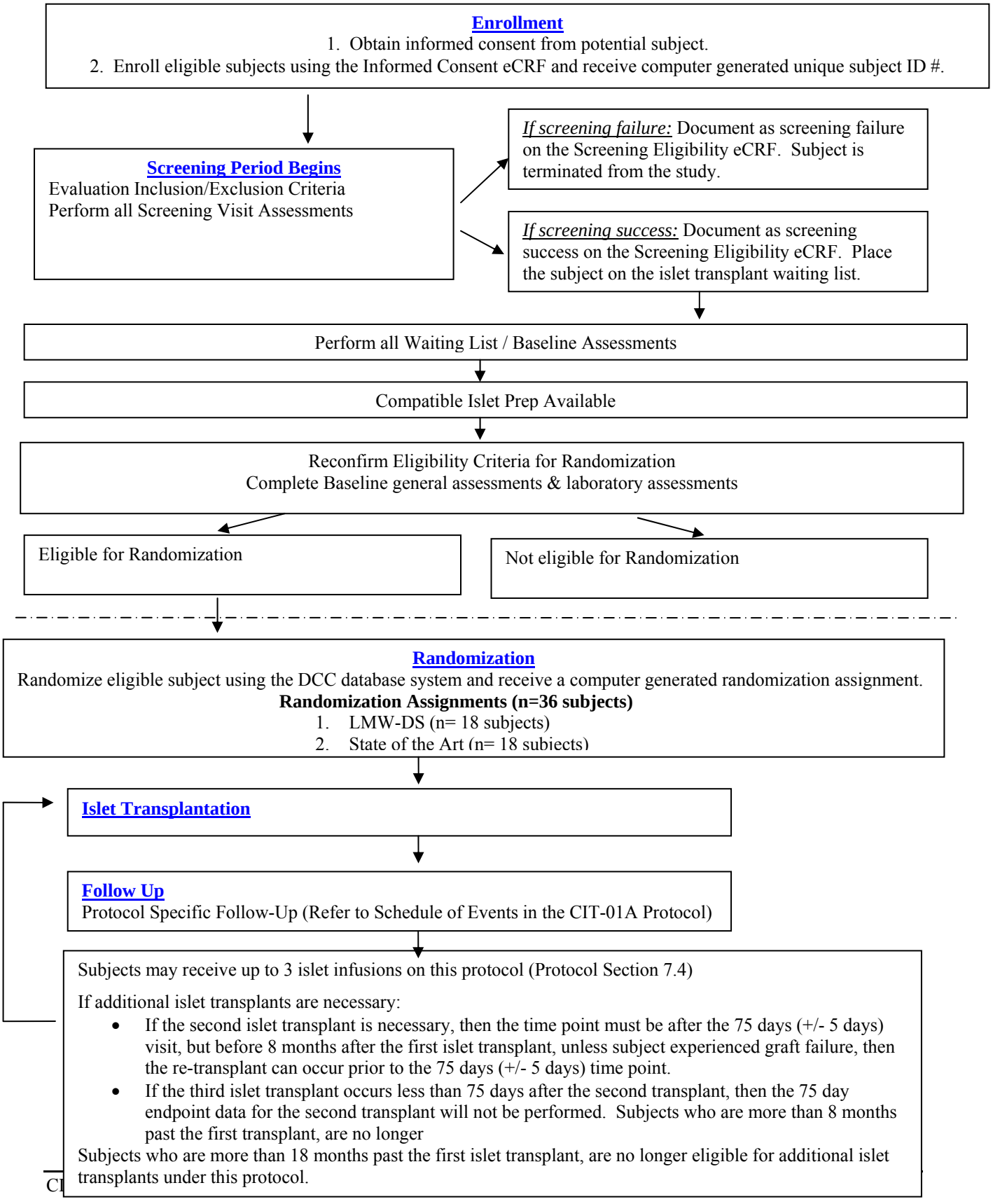
1.10. Scandia Transplant List

The UNOS equivalent in Sweden is Scandia Transplant. They control the waiting list for solid organ transplant. However, the wait list that is used for islet transplant is through the Nordic Network, which comprises the islet transplant centers in Sweden, Norway, Denmark, and Finland. The Scandia Transplant offers organs to the Nordic Network (organs come from Sweden, Norway, Denmark and Finland), and the wait list for the islets is controlled through the islet isolation lab in Uppsala at the University of Uppsala-Rudbeck Laboratory. Once a pancreas becomes available, the islets are selected to go to the next suitable person on the Nordic Network waiting list- whether that person is a CIT-01 subject or not.

2. Study Design

2.1 Study Design for CIT-01



2.2 Screening, Waitlist/Baseline, and Randomization Procedures

2.2.1 Informed Consent, Screening, Waiting List/Baseline

INFORMED CONSENT:

Each subject must provide written informed consent prior to undergoing any study-specific CIT-01 screening evaluations. Refer to the instructions for obtaining consent (MOP Section 1.6.1)

SCREENING:

After the subject has signed the consent form, s/he will undergo CIT-specific screening procedures to determine eligibility for the study. 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 IoR form).

Tests conducted within the time window identified below will be considered current for screening purposes.

Screening Assessments	Allowable timeframe prior to the date of consent
EBV IgG	*No limit. Positive test result required for eligibility*
Retinopathy evaluation; Physical exam; Chest x-ray; Abdominal Ultrasound; ECG; Myocardial Scintigram; Conduction Velocity and RR intervals; Serology (HIV, Hepatitis B, Hepatitis C); CMV IgG and IgM; Coagulation Status(APTT, PK, fibrinogen, platelets)	*Within one year*
CBC w/ differential; Serum Chemistry Panel and CRP; Urine Albumin; Fasting Lipid Profile (Total, LDL, HDL, Triglycerides); GFR	*Within 6 months*
Quality of Life Questionnaires; Medical and Diabetes History Assessment; Panel Reactive Antibody (Alloantibodies); Record recipient HLA and Blood Type;Pregnancy Test; HBA1c; MMTT; FSIGT; LI; HYPO; Clarke Score; c-peptide to Glucose Creatinine ratio; Serum to Archive; PBMC and Plasma to Archive; RNA to Archive.	*After informed consent has been obtained*

Local Labs: Sites should complete all local screening procedures, including instructing the subject on how to complete the CIT Blood Sugar Record and HYPO source documents and collecting this data for at least one month, **prior to conducting any centrally assessed screening tests.**

a. If the subject is no longer eligible after completing the local screening procedures, the subject is considered a "Screening Failure". The site should access the *Screening 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.

b. If the subject still appears eligible after completion of local tests, the site should complete the central lab screening tests.

Central Labs:

a. If the subject is ineligible after receiving the central lab results, the subject is considered a "Screening Failure". The site should access the *Screening 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.

b. If the subject is confirmed to be eligible for the study after completion of all local and central screening tests, the subject is considered a "Screening Success". The site should access the *Screening Eligibility* eCRF, complete and "submit" the form.

The screening period ends when all information/results needed for evaluation of inclusion and exclusion criteria are available.

If the subject meets eligibility criteria, the subject should be placed on the waiting list for transplantation. A general waiting list for all subjects enrolled in the study will be kept at the Rudbeck Laboratory in Uppsala, Sweden.

The subject may be enrolled in the study using the DCC electronic data entry system. Enrollment into the study is done by completing the *Informed Consent eCRF* and the *Screening Eligibility* **eCRF** located on the CIT website (www.isletstudy.org). The CIT website can be accessed using any computer connected to the Internet. Authorized personnel will be required to log-in to the system using their assigned user identification and password.

Once the date on which the enrollment 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 is 7-characters in length and unique to each subject. The format of the unique Subject ID is as follows:

1A - N N - N N N

The number is broken down as follows:

- **1A or 1B** = number used to indicate the protocol the subject has consented and is eligible to participate
- N N = 2-digit code for the center-ID number**.**
    - **Your 2-digit center ID number is:__ ___**
- N N N = 3-digit number assigned sequentially based on site enrollment

REQUIRED DOCUMENTATION: The Study Coordinator should document in the subject's source documents that the subject met enrollment criteria and was enrolled into the CIT-01study.

WAITING LIST /BASELINE:

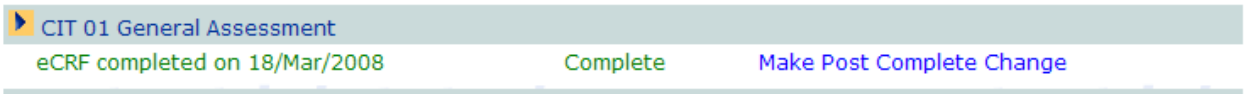
Once it is confirmed that a subject meets all screening eligibility criteria, s/he should be placed on the islet transplant waiting list. The Waiting List / Baseline Visit (WL/BL - Visit 02) on the SOE begins when the subject is placed on the transplant waiting list and continues through Day -1.

WL/BL assessments that are conducted only once (marked by a stand-alone "X" on the SOE) should be completed when a subject moves from screening to WL/BL or when it is convenient for the subject to return based on the need for repeat assessments. All WL/BL assessments must be conducted prior to the start of immunosuppression. The results from

these tests are considered baseline results that will be used to reconfirm eligibility prior to randomization. These results should be recorded on the Visit 02 eCRFs.

Most of the assessments listed in the WL/BL 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, HbA1c is listed as "X-q6mo"; therefore, all subjects should have blood drawn and sent to the central laboratory every 6 months while on the waiting list.

The results of each repeat assessment should be entered into the corresponding Visit 02 eCRFs. For example, a Chest x-ray must be conducted yearly, according to the SOE. When an initial Chest x-ray is conducted and the results are entered into the *General Assessment eCRF*, a second *General Assessment eCRF* will become available (see below). Within the eCRF listing in the CIT database, you will see the completed eCRF (November 9, 2007) and link to add a new *General Assessment eCRF* one year later ("Enter New eCRF").



Waitlist Assessments	Timetable for repeat testing while on the waiting list
Retinopathy Evaluation; Physical Exam; Chest x-ray; ECG; Coagulation Status (APTT, PK, fibrinogen, platelets); CGMS; Serology (HIV, Hepatitis B, Hepatitis C)	Once a Year
CBC with differential; Serum Chemistry Panel; Glycemic Lability -LI (repeat only if used as an inclusion criteria); Glycemic Lability (MAGE); Alloantibodies; Quality of Life Questionnaires (SF36, DTSQ); HbA1C; Blood Sugar Records and Hypo sheets; Full Hypo Score; Clark Score	*Once every 6 months*
Baseline Assessments	
Re-evaluation of the eligibility criteria; Record concomitant medications; CMV and EBV by PCR; Autoantibodies; RNA and Plasma to Archive, Alloantibodies; Physical Exam; CBC with differential; Serum Chemistry Panel; Coagulation Status (APTT, PK, fibrinogen, platelets); Blood Sugar Records and/or Hypo sheets; Serology (HIV, Hepatatis B; Hepatitis C); Chest x-ray; ECG Crossmatch; Serum Pregnancy Test; HbA1c	*At the time the pancreas becomes available, prior to transplant*

2.2.2 Randomization

Once a compatible islet donor preparation is available and the re-evaluation of eligibility criteria has been confirmed, then the site personnel may randomize the participant using the DCC electronic data entry system *(www.isletstudy.org)*.

Randomization Eligibility Form: Participants will be randomized using the DCC electronic data entry system.

- If the subject is no longer eligible, the site should access the *Randomization 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 randomization, the site should access the *Randomization Eligibility* eCRF, complete and "submit" the form. Once the form is submitted, the system will display a prompt that confirms the intent to randomize the subject. Once the site confirms the intent to randomize the subject, the subject will be assigned to a treatment arm.

REQUIRED DOCUMENTATION: The site personnel should print the screen that provides the randomization assignment and place this information in the subject's clinic record. The Coordinator should document in the subject's source documents that the subject met enrollment criteria and was randomized to "LMW-DS" or "State of the Art".

2.2.3 Back-Up Randomization Procedures

In order to provide a back-up process that can be used when the on-line randomization system is not available, the DCC will provide each participating site with two back-up randomization envelopes. These envelopes will be opaque and will have a sequence number printed on the outside. Each envelope will contain a random treatment assignment. These envelopes should be stored in a secured location, where they are also readily available to those responsible for randomizing a subject into the study.

In the event that a site is ready to randomize an eligible subject and the on-line randomization system is not available, the delegated site personnel will obtain the numbered back-up randomization envelope. The site personnel should select the envelope with the lowest sequence number first.

Note: Once an envelope has been opened, the patient will be considered randomized and will be included with the intention to treat population.

The clinical site must report the use of each back-up randomization envelope to the DCC within one working day.

- The DCC PC should be contacted within 24 hours of using a back-up randomization envelope.

  University of Iowa
  Clinical Trials Statistical & Data Management Center
  Traci Schwieger, Protocol Coordinator
  Phone: +1-319-384-4180
  Email: traci-schwieger@uiowa.edu

- A copy of the back-up randomization reporting form (Appendix 2) should be faxed to the DCC at +1-319-335-6580, Attention Traci Schwieger.

- The original version of the back-up randomization form (the form you received in the back-up randomization envelope) and Back-Up Randomization Reporting Form should be maintained as the source documents in the subject's clinic research files.

  Once the DCC has been informed that a back-up randomization envelope has been opened, it will temporarily suspend randomization for that site. The purpose for this temporary suspension is to adjust the randomization sequence for that site so that a temporal balance will be maintained. The DCC will adjust the sequence within three working days and will immediately notify the clinical site that it can again randomize subjects using the electronic data entry system. In the event that a second randomization assignment is needed during the temporary suspension period, the site personnel may use the second back-up randomization envelope provided by the DCC.

The DCC will send the clinical site replacement back-up randomization envelopes containing a new randomized treatment assignment.

3. Instructions for Study-Specific Procedures

3.1. Crossmatch

Banked serum (up to 60 days old) may be used for crossmatch testing as long as the subject has not experienced a transfusion of blood products during that 60-day period. If banked serum is used for crossmatch testing, the testing need not be repeated upon admission unless the subject has experienced a blood products transfusion.

3.2. Etanercept Dosing (Experimental and State of Art arms)

The protocol specifies a dose of 50mg 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.

3.3. ATG Administration (Experimental and State of Art arms)

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

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

If, for practical reasons, three doses cannot be administered before transplantation the first and second will be administered on day -1 and 0 and the three remaining will be administered on day +1, +2, +3.

Day	Hour	Activity	Infusion Time	Dose
-2/-1	21:00 -09:00	Admitting the patient, pre-op investigations, pulm, X-ray etc		
-1/0	**09:00 – 17:00**	**Thymoglobulin dose nr 1**	**8 h**	**0.5 mg/kg**
-1/0	17:00 – 23:00	At least 6h rest from Thymoglobulin		
0	23:00 – 0:500	Thymoglobulin dose nr 2	6 h	1.0 mg/kg
0	c:a 11:00	Patient to angio for portal catheter placement		
0	c:a 12:00	Islet transplantation		
+1	**09:00 – 15:00**	**Thymoglobulin dose nr 3**	**6 h**	**1.5 mg/kg**
+2	**09:00 – 15:00**	**Thymoglobulin dose nr 4**	**6 h**	**1.5 mg/kg**
+3	**09:00 – 15:00**	**Thymoglobulin dose nr 5**	**6 h**	**1.5 mg/kg**

In cases in which the initial transplant does not occur, maintenance immunosuppression should be restarted according to protocol sections 5.7 through 5.8 once another organ becomes available. Investigators should use clinical judgment to determine the appropriate induction regimen for subjects in this situation. 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 an organ 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) transplant. In cases in which more or less ATG has been administered, investigators should use their discretion to adjust ATG administration accordingly.

For Basiliximab Induction:
Should an islet product become available within 4 days of the first dose of Basiliximab, then the subject will continue with the original schedule of induction with Basiliximab. If an adequate islet product does not become available within 4 days of the first dose of Basiliximab, t hen once an adequate islet cell product is available, the subject will start a new series of 2 doses of Basiliximab.

3.4. Heparin Administration (State of Art arm only)

The protocol describes the administration procedures for heparin.

3.5. 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.

3.6. Checklist for Inclusion/Exclusion Criteria

A checklist to assist subjects' eligibility based on inclusion/exclusion criteria are included in Appendix 13. 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 on the bottom is a simple way to document that a subject meets all inclusion/exclusion criteria, as described in Sections 2.3. 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.

3.7. 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 IOR). 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.

3.8. Glucometer Quality Control (QC)

Subjects will record their blood sugar readings 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 quality control should be implemented both by the subject and the site study coordinator.

3.8.1 Subject QC

The site study coordinator should instruct the subject to follow the quality control instructions outlined in the glucometer package insert. Provide the subject with the following reminders upon receipt of 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 study coordinator if they continue to receive test results outside the expected range.

3.8.2 Study Coordinator QC

The site study coordinator 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.

3.8.3 Downloading Glucometer Information

The software for the One Touch glucometer will be provided to each center. The software is very user-friendly. When the user opens the software for One Touch s/he 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 the meter is blue, turn it OFF before downloading, if the meter is gray, turn it ON before downloading.

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

3.8.4 Use of Lifescan Ultra Glucometers

Lifescan Ultra 2 glucometers are available to subjects through a Clinical Trials Agreement between NIH and Lifescan or arrangements can be made through the site's Lifescan representative. 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 t his 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 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 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 test 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. See Section 9 for instructions regarding sending malfunctioning glucometers to DCC. 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.

3.9. Continuous Glucose Monitoring System (CGMS)

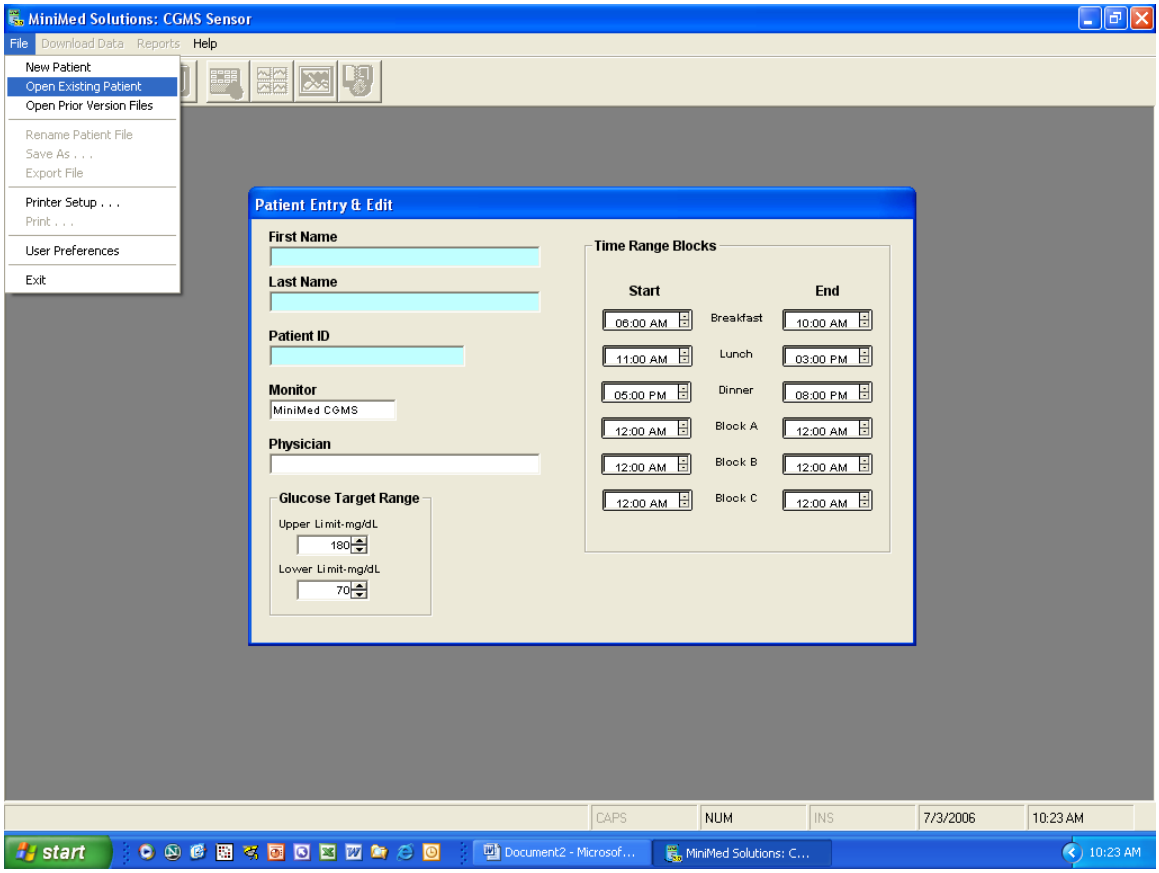
CIT provides clinical sites with CGMS Gold or IPro monitors for sue in the CIT studies. These units should be used to collect t he data for the 72-hour periods described in the protocol SOEs. However, if a subject is already using a different CGMS within the Medtronic family (Gold, IPro or Paradigm), 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. The investigator or designee 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 study coordinator on how to rename the CGMS .mmg files, removing subject identifiers, before transferring them to the DCC.

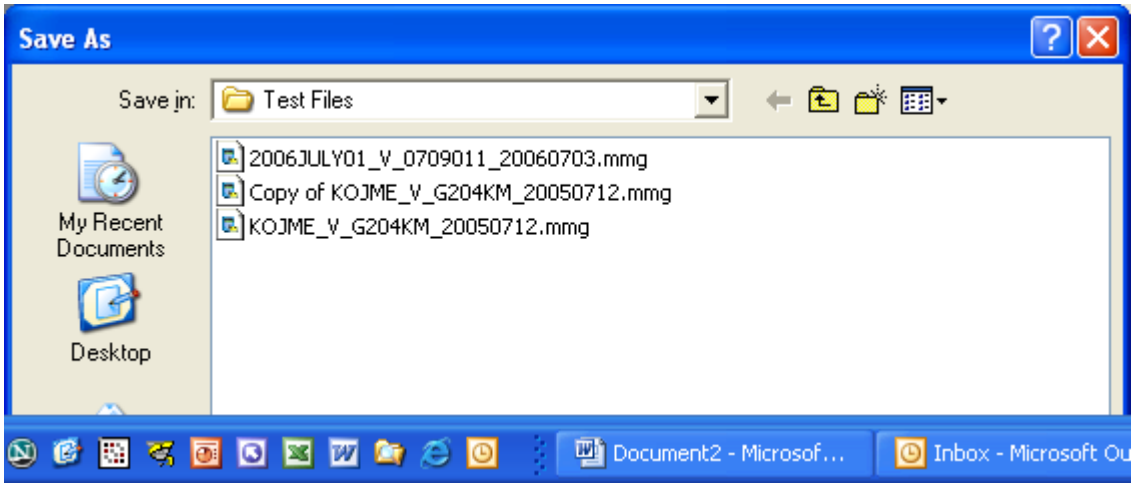
3.9.1 Renaming and Transferring mmg Files to the DCC

When the coordinator is ready to send a data file to the DCC, s/he 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.

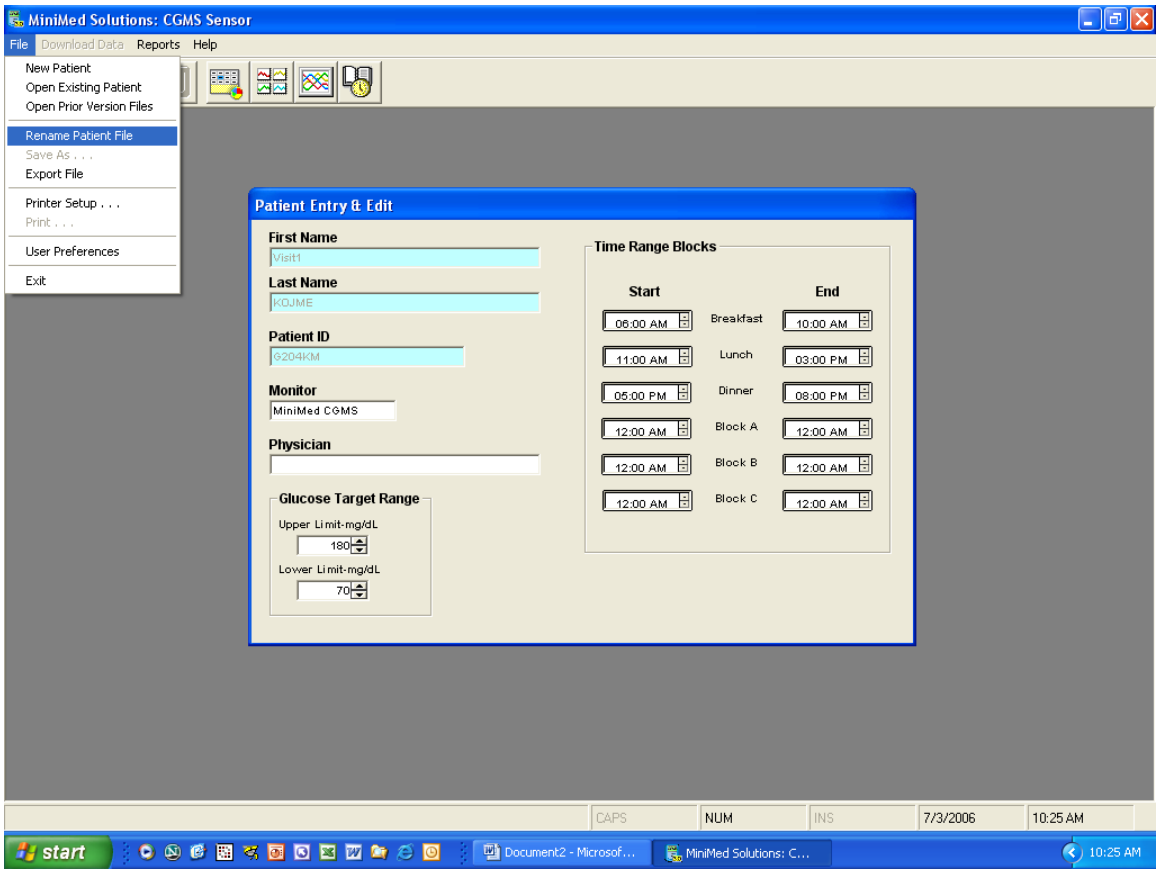


The user should select the "open existing file" option from the file menu and select the file to be sent to the DCC.

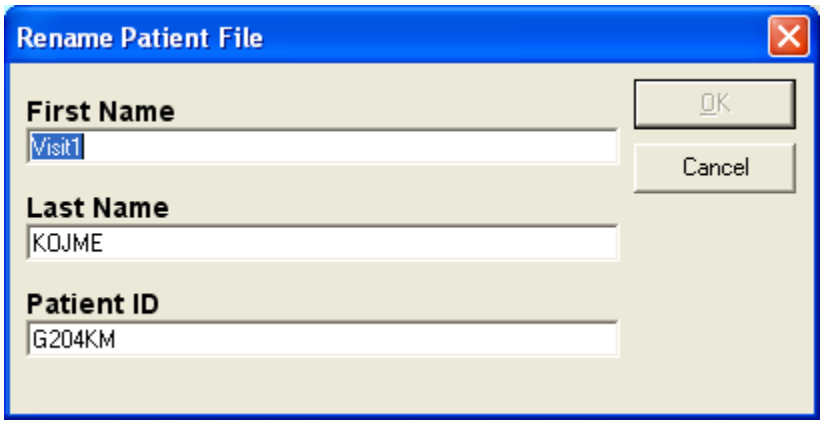


Files with the "mmg" extension will be sent. There are three listed here. The user will be required to navigate to the correct folder on his/her computer to find these files. The location of the folder depends on how the software was installed.

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

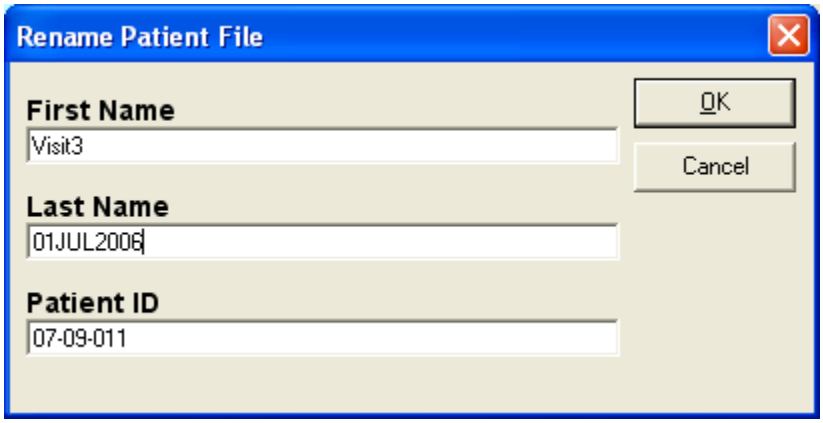


The user will then see the following window that reflects the name and ID used to create the subject. This information can be anything you want it to be. The user must change the values for the three fields before sending the file to the DCC.



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

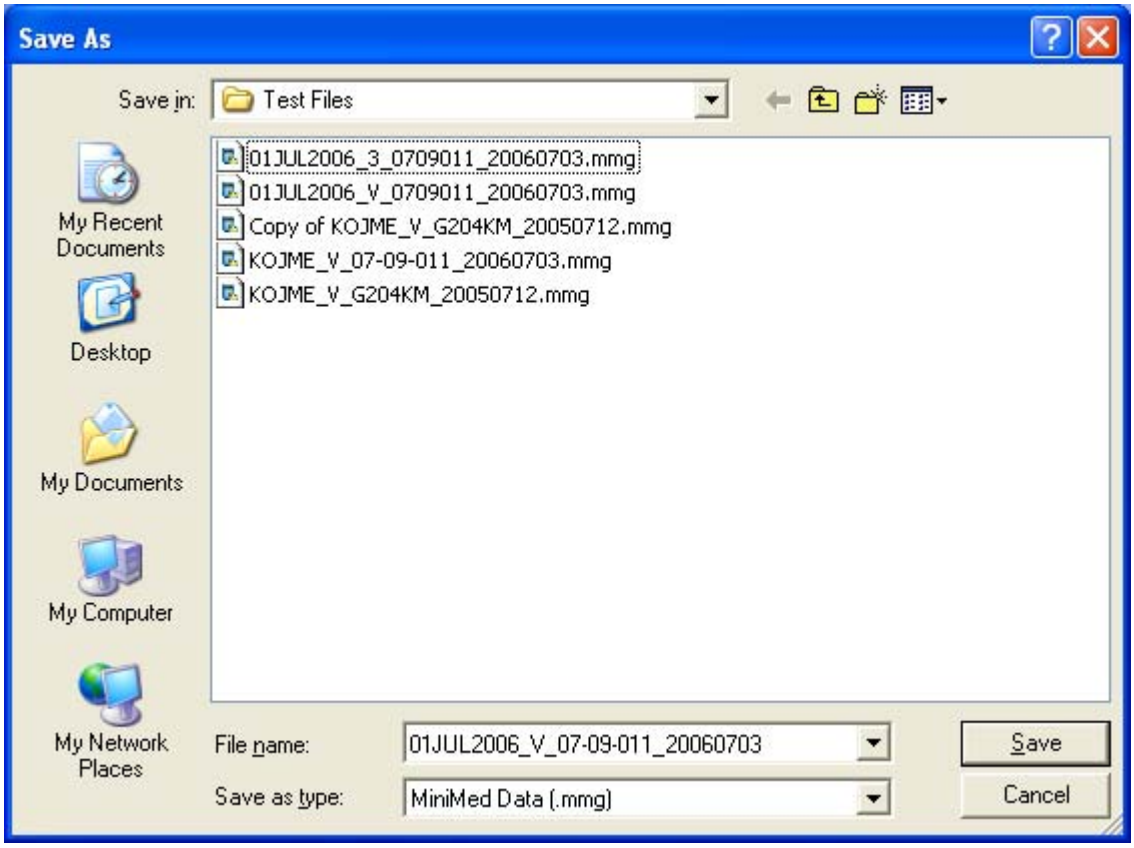
identifying information. The software uses the data entered in the last name field, first letter of the First Name field, and Patient ID field, and then adds the date the file was renamed to build a new file name (you will not lose the old file). Please enter the Visit Number from the SOE in the "First 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 provided in the previous window. In this case, the 01JUL2006 was provided in the Last Name field, _V_ is there because the user 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 the 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.

3.10. Instructions for Laboratory Procedures

3.10.1 Repeating Fasting Serum 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-01 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 repeat samples.

3.10.2 Archived Serum Samples and Genetic Testing

As part of the informed consent process, subjects can decline (in writing) to have serum samples stored and/or to have samples used for future genetic testing. If a subject declines to have serum samples collected and stored for future research studies, the sites should not collect the RNA to archive, serum to archive or PBMC/plasma to archive samples. If a subject declines to have blood samples collected and stored for future genetic (i.e., DNA) testing, then RNA, serum and PBMC/plasma to archive samples can be drawn, but the repository will note that the PBMC samples may not be used in the future for DNA extraction.

3.11. 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 *Randomization Eligibility eCRF*; it confirms, using the most recent results available, that the subject is eligible to receive a second or third islet infusion.

All subsequent transplant 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.

3.11.1 Second Transplant

The protocol indicates 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 75 days post first islet infusion if s/he meets the additional eligibility criteria outlined in the protocol. Site should ensure that these criteria are met and documented in the chart. Please refer to Figure 1: Second Transplant Qualification: Subjects with Partial Graft Function. A source tool for documenting eligibility for a second transplant is included in Appendix 16.

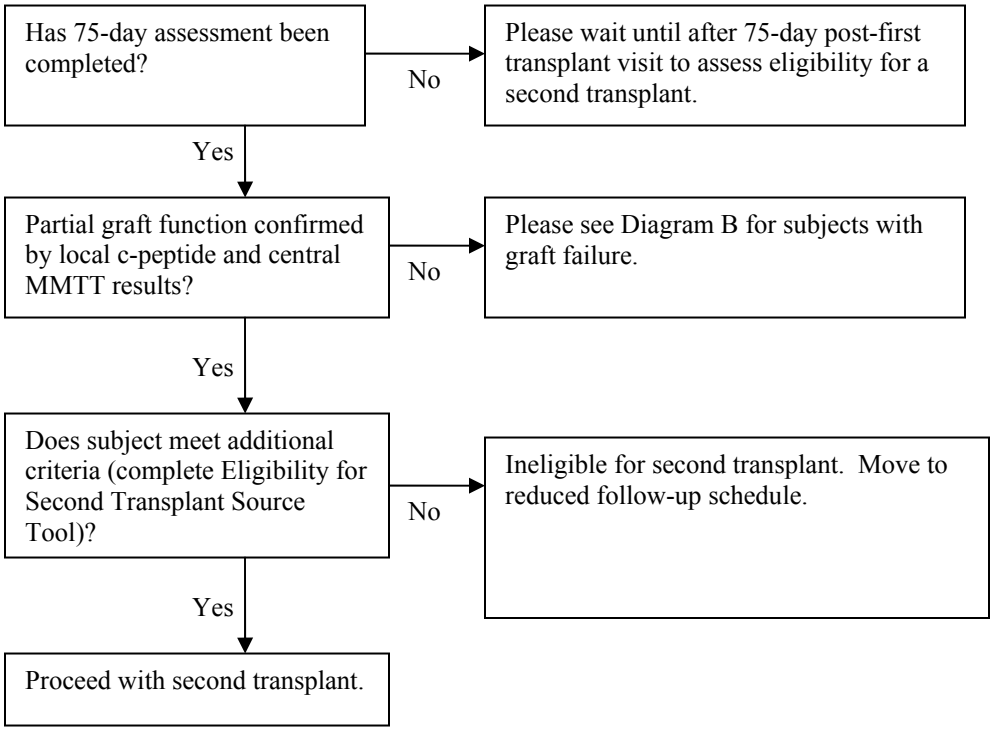


Figure 1: Second Transplant Qualification: Subjects with Partial Graft Function

- Subjects with **graft failure** can receive a second transplant with Steering Committee approval. These subjects are not required to wait for day 75 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 and the Protocol Chair: Please refer to Figure 2: Second Transplant: Subjects with Graft Failure. A source tool for documenting eligibility for a second transplant is included in Appendix 16.
  - Results of graft failure assessments (see protocol for specifics)
  - Post-transplant clinical data
  - Potency testing from 1st transplant product
  - Additional assessments as requested by the Steering Committee

  Before Day 75, the DCC will circulate the data to the Steering Committee (SC) for review. The site can move forward with the second transplant once the site receives written confirmation to re-transplant from the DCC.

  After Day 75, the Protocol Chair will circulate the data to the Nordic Network Steering Committee (NNSC) for review. A teleconference will be arranged within one week to decide on the issue. The site can move forward with the second transplant once written confirmation of the NNSC decision has been received. The decision of the NNSC will be provided to the sponsor via e-mail from the Protocol Chair (see Appendices 19 and 20 for e-mail templates).

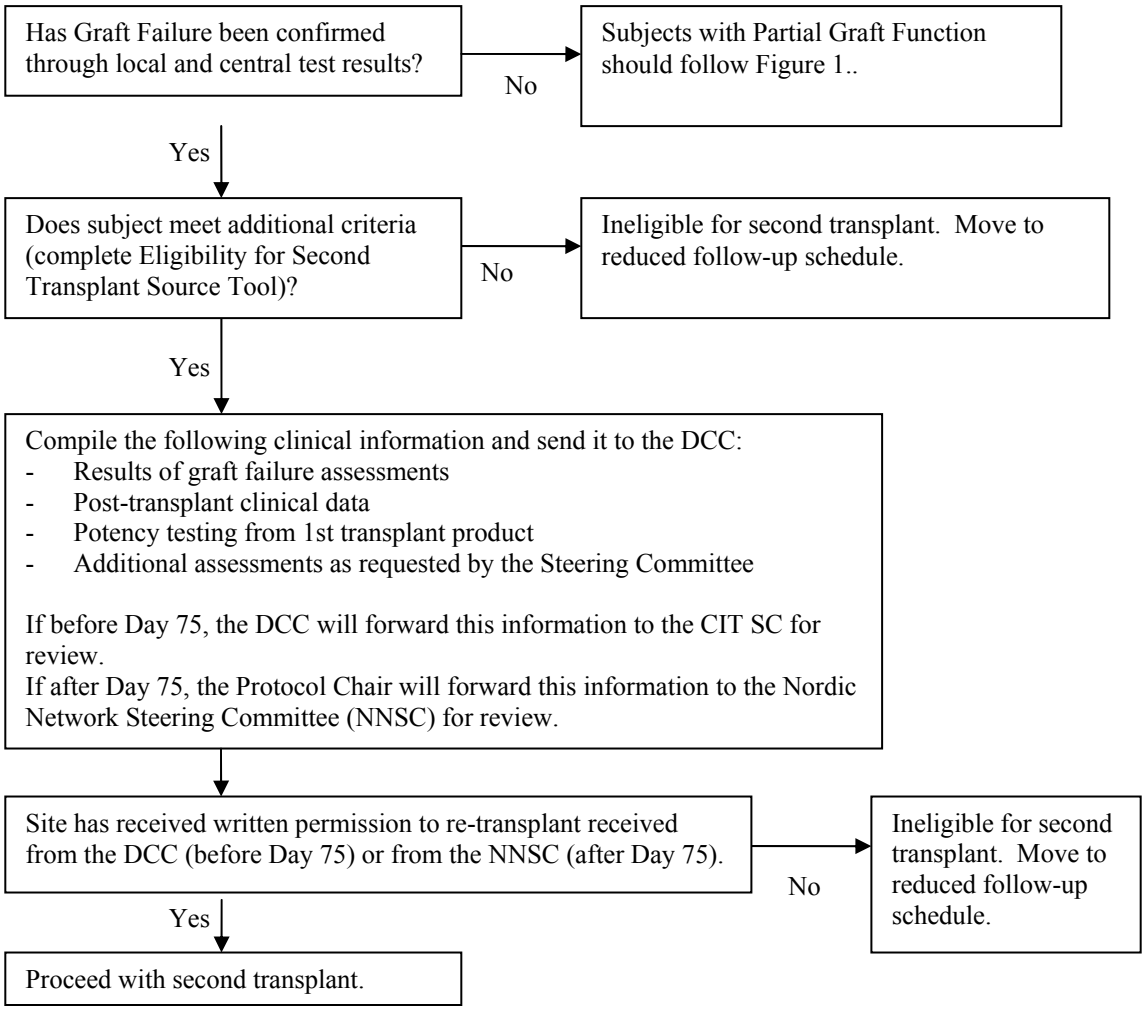


Figure 2: Second Transplant: Subjects with Graft Failure

3.11.2 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 3: Third Transplant Qualification. A source tool for documenting eligibility for a third transplant is included in Appendix 17.

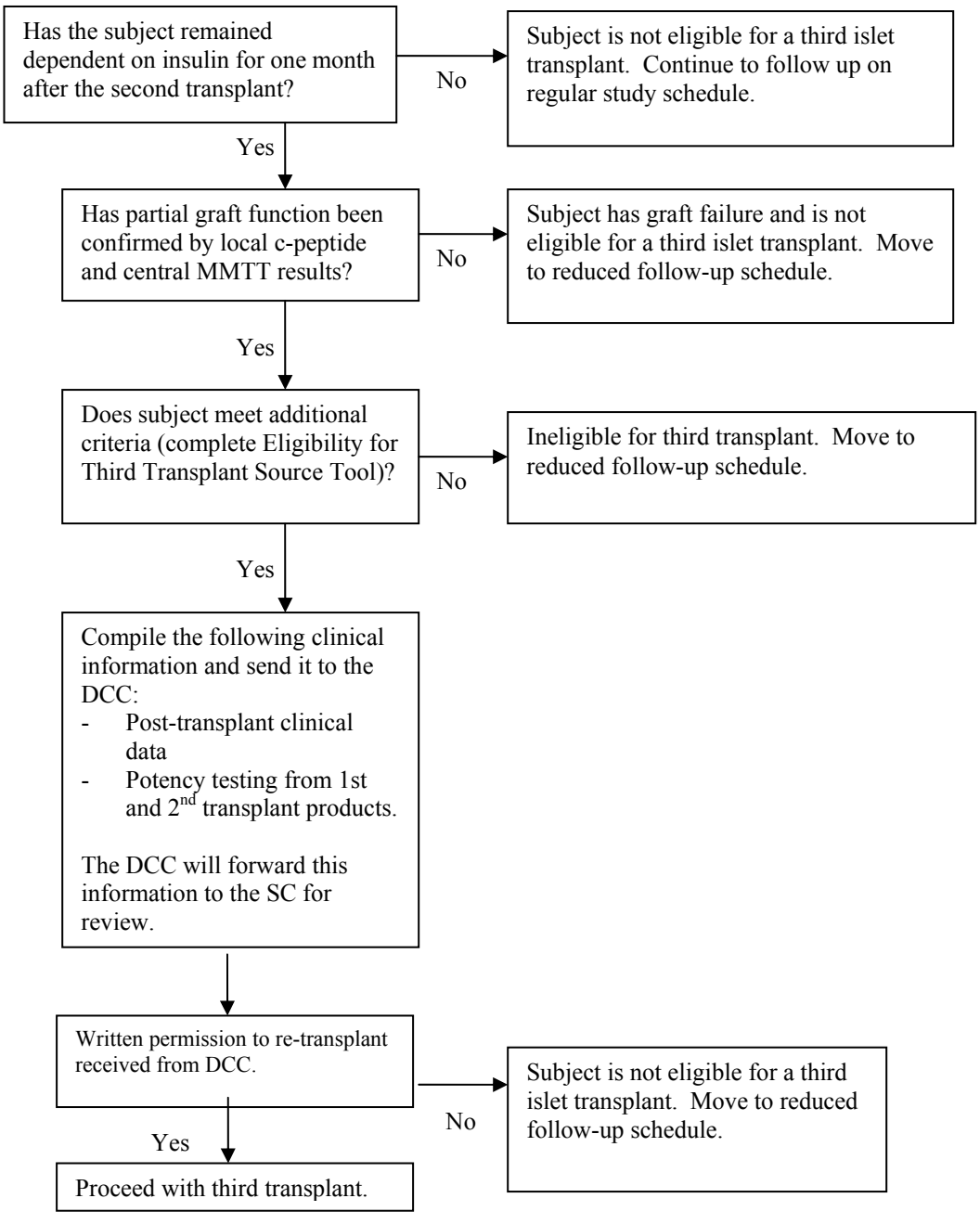
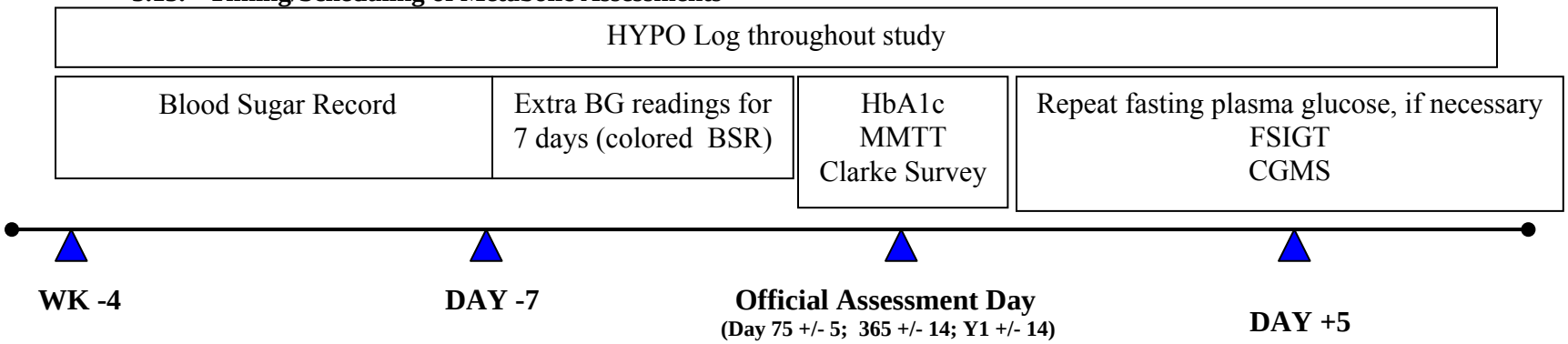


Figure 3: Third Transplant Qualification

3.12. End of Study Assessments

Some assessments are required at both Day 365 and Day 365 Post-Initial Transplant on the schedule of events. If a subject receives only one islet transplant as part of his/her participation in CIT, Day 365 and Day 365 Post-Initial Transplant 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 Day 365 visit, but none of the assessments listed in both columns needs to be performed twice.

3.13. Timing/Scheduling of 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 and MMTT Assessments on the official assessment day.
3. Complete the Clarke Survey on the official assessment day for 75, 365, & Y1 only.
4. Collect the Blood Sugar Record and Hypoglycemia Sheets 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).
5. Repeat the fasting serum glucose if the result from the MMTT is > 126 mg/dL. Perform a 2^{nd} repeat if the 1^{st} repeat result is ≤ 126 mg/dL.
6. Complete the FSIGT within 5 days after the official assessment day for Day 75, 365, & Y1 only.
7. Start the CGMS within 5 days after the official assessment day for Day 75, 365, & Y1 only.

4. Specific eCRF Instructions

4.1 Blood Sugar Record 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 for the previous 28 days, 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-01protocol). 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 14 (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 documents recordings, determination of the subject's actual insulin requirements, and/or inspection of the glucometer download data. The data entered on the eCRF must exactly match the subject's source documents; therefore, any changes made to the source documents, as a result of subject discussions with the study staff, must be initialed and dated by the subject and the study coordinator.

Individual insulin doses will not be entered into the *Blood Sugar Record and Hypoglycemic Events eCRF*. Instead, the study coordinator will total the individual doses for each recorded day and enter the daily totals into the *Blood Sugar Record and Hypoglycemic Events eCRF*. Study monitors will verify total daily insulin dosages.

If it is determined that insulin source data for a particular day is inaccurate, incomplete, or unreliable, the coordinator should draw a line through the insulin data for that day and initial and date the correction on the source document. The coordinator will mark N/A on the corresponding eCRF data field.

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 document into the *Blood Sugar Record and Hypoglycemic Events eCRF* for the timepoints indicated on the SOE. In addition, ALL hypoglycemic events from all Blood Sugar Record source documents the subject completes must be entered into the *Blood Sugar Record and Hypoglycemic Events eCRF*.

4.1.1. Blood Sugar Records and the Full HYPO Source Document

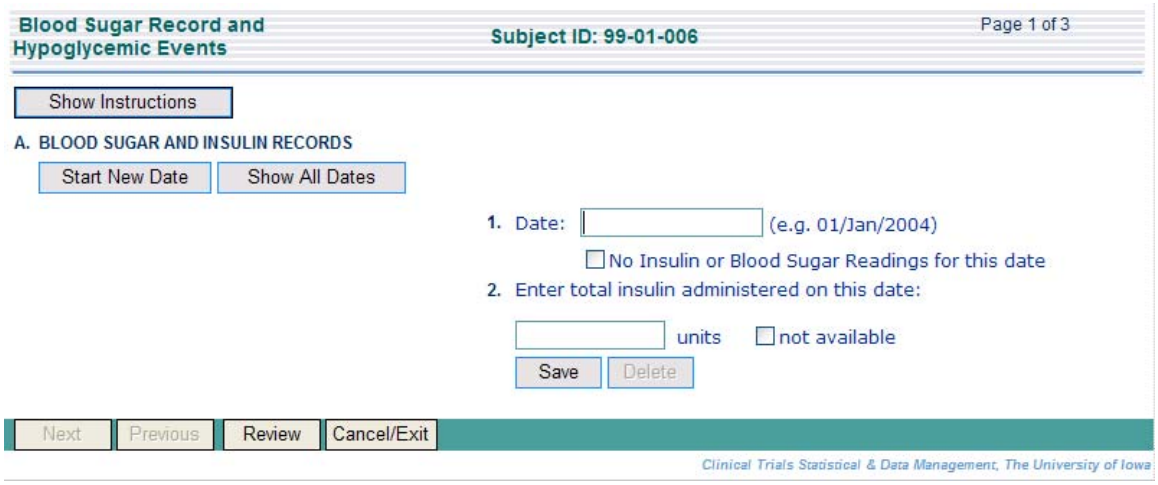
The data from the Blood Sugar Record and HYPO source documents will be entered into the *Blood Sugar Record and Hypoglycemic Events eCRF*, which is located in the Event-Driven Forms section in each subject's set of eCRFs. All blood sugar records and HYPO events will be added to a growing table that will 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 Score eCRF*. This eCRF is available at the Y1 visit.

4.1.2. Entering Dates and Insulin Usage

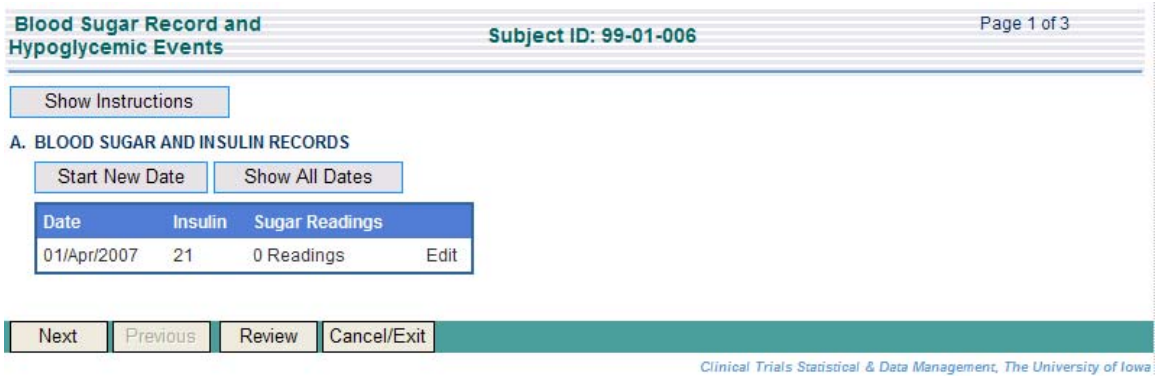
To start entering blood sugar data on page 1 of the eCRF, click on the "Start New Date" button. In Section A1, enter the first date on the Blood Sugar Record source document. If no blood sugar readings or insulin usage were recorded on that date, click in the checkbox next to "No Insulin or Blood Sugar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



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

If insulin usage was **not recorded** (*i.e.*, all of the insulin blanks on the source doc for that day are blank) but there are some blood sugar readings to be entered, click in the checkbox next to "not available".

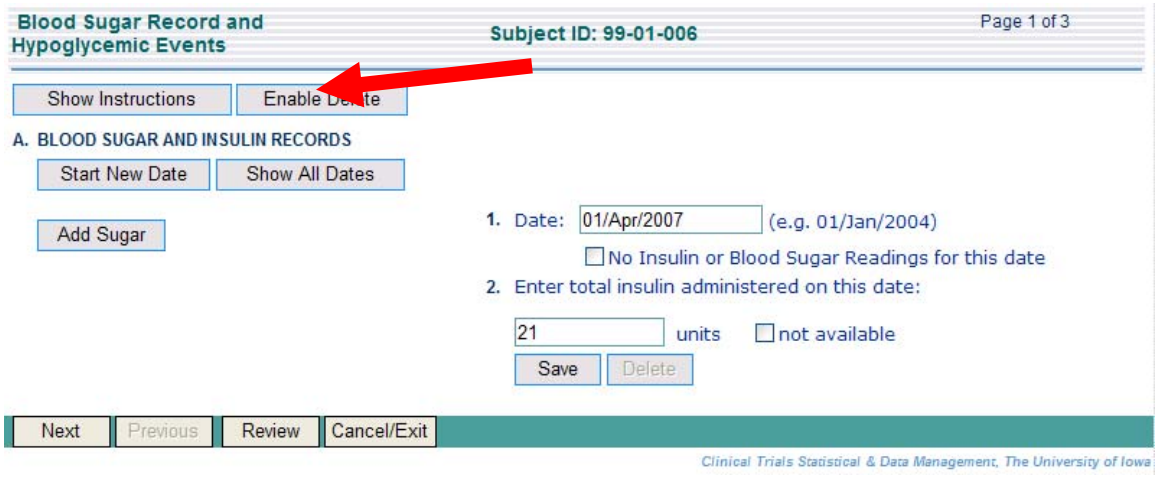
If the subject is not receiving insulin, insulin should be recorded as 0 units. Enter 0 in the text box next to "units".



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.

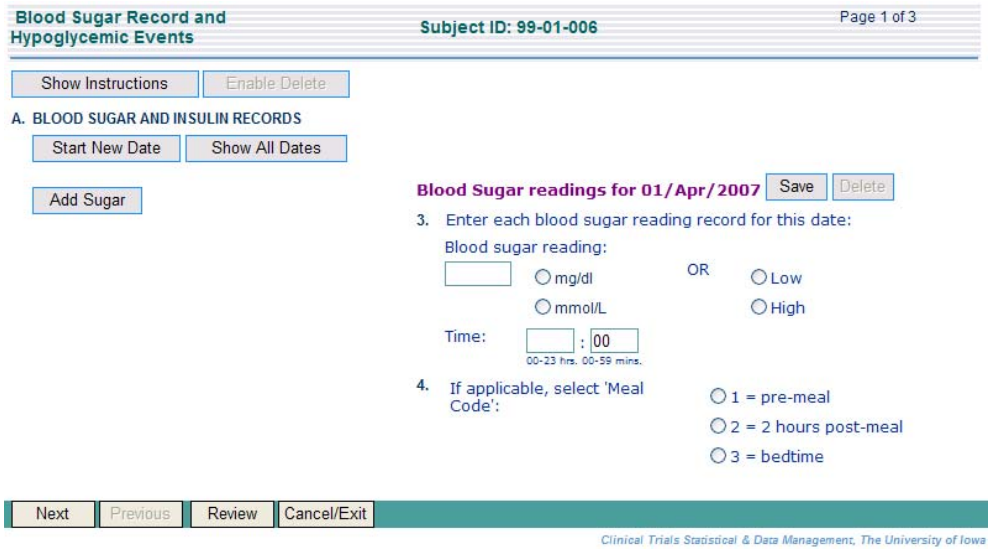
Correcting Errors: If you make a mistake in a date or insulin entry, click on "Edit" in the row for the date on which you need to make changes (in the table displaying the dates and insulin usage). This will take you back to Sections A1 and A2, where you can change your entries. When you are done changing 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 greyed out until you click on "Enable Delete".



4.1.3 Entering Blood Sugar Records

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.

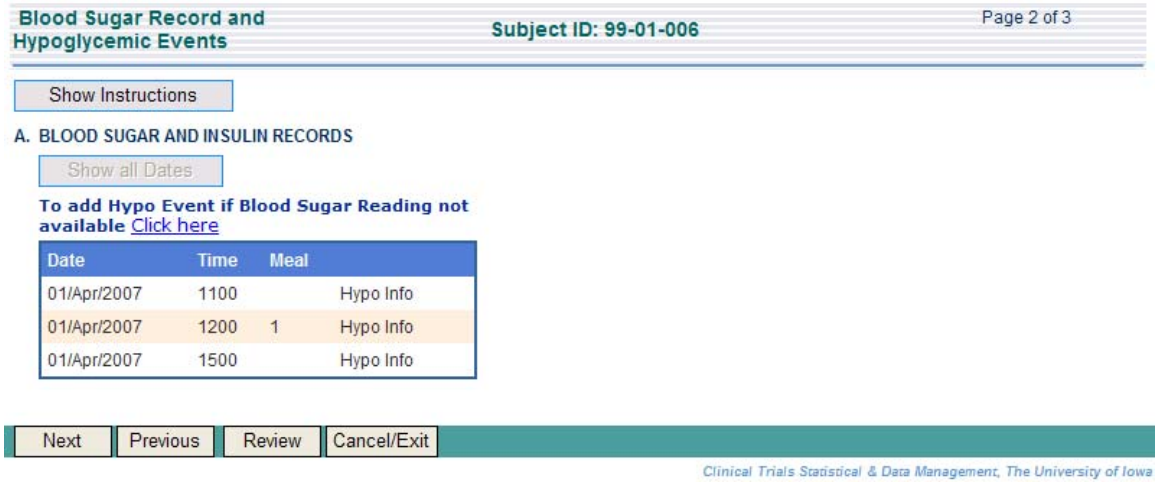
Correcting Errors: If you make a mistake in a blood sugar entry, click on "Edit" in the row with the blood sugar reading you need to change (in the table of blood sugars). Here you will be able to change the blood sugar reading, the time or the meal code. Click the "Save" button when you are done.

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 greyed out until you click on "Enable Delete".

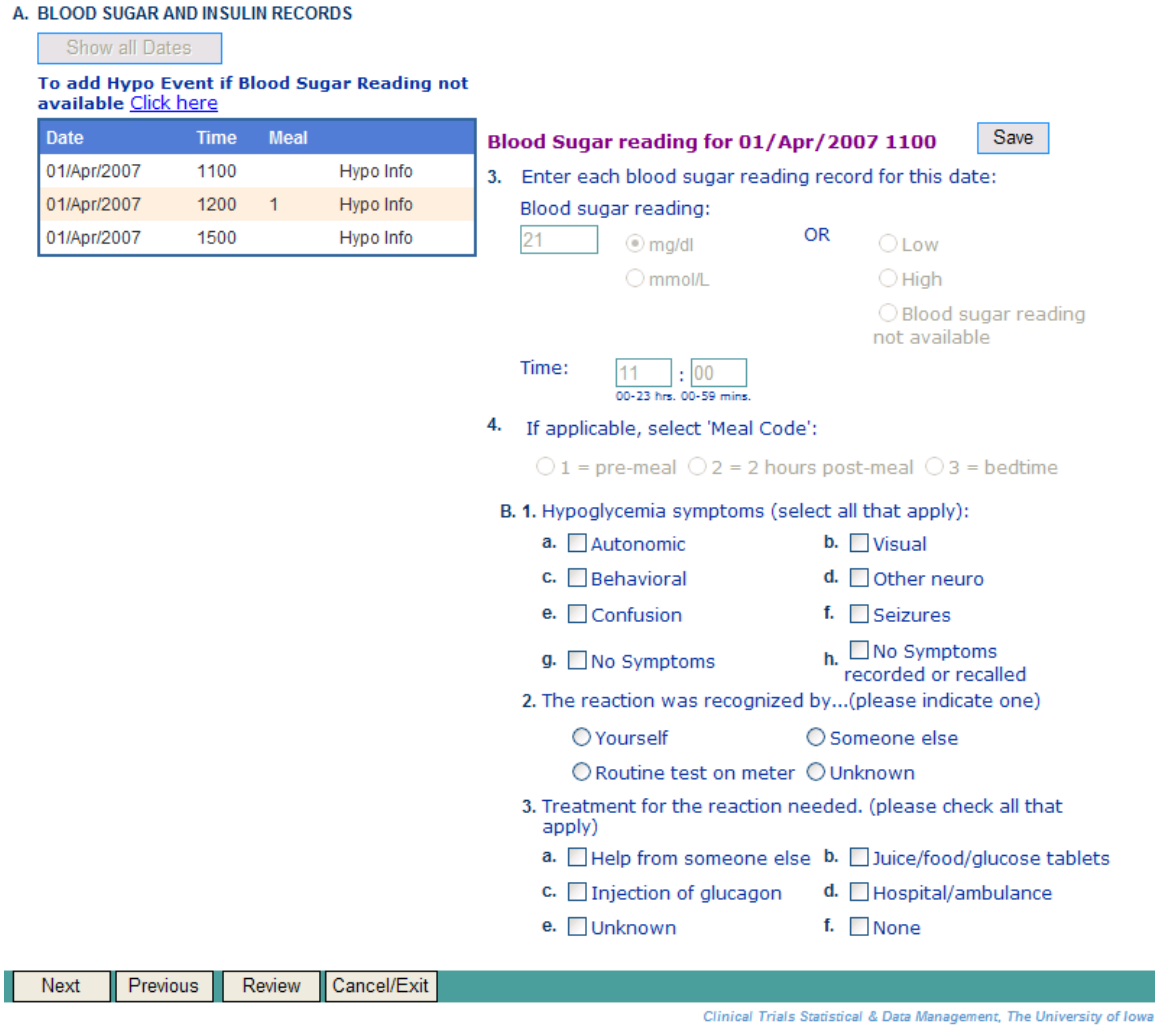
When you have entered all of the blood sugar readings and insulin usage information from the Blood Sugar Record source document, click the "Next" button at the bottom left of the page.

4.1.4 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.

4.1.5 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*.

4.1.6 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 4.1.3).

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"

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

4.2 Reporting Hypoglycemic Events

A severe hypoglycemic event is defined in the CIT-01 protocol 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).

Hypoglycemic events may be reported on either or both of two eCRFs:

- *Blood Sugar Record and Hypoglycemic Events* eCRF: *All* hypoglycemic events recorded throughout the study should be reported on this eCRF, and the HYPO log should be completed for each event.
- *Adverse Event* eCRF: If a participant experiences a hypoglycemic event with any of the characteristics of a serious adverse event (note: this is different from a severe hypoglycemic event), the event should be reported on the *Adverse Event* eCRF in addition to the *Blood Sugar Record and Hypoglycemic Events eCRFs*.

4.3 Laboratory eCRF

The *Laboratory* eCRF is divided into sections based on different types of tests: coagulation status, hematology, serum chemistry, fasting lipid panel and urine studies. 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.

4.4 Concomitant Medications eCRF

The coordinator should begin filling out the *Concomitant Medications* eCRF as soon as the subject begins to receive study medication. 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 1.9.3.1 for instructions on recording insulin usage.

If ciprofloxacin, *other than that given in the islet infusion bag*, is administered to a subject, it should be entered into the *Concomitant Medications eCRF*.

4.5 Islet Transplant eCRF

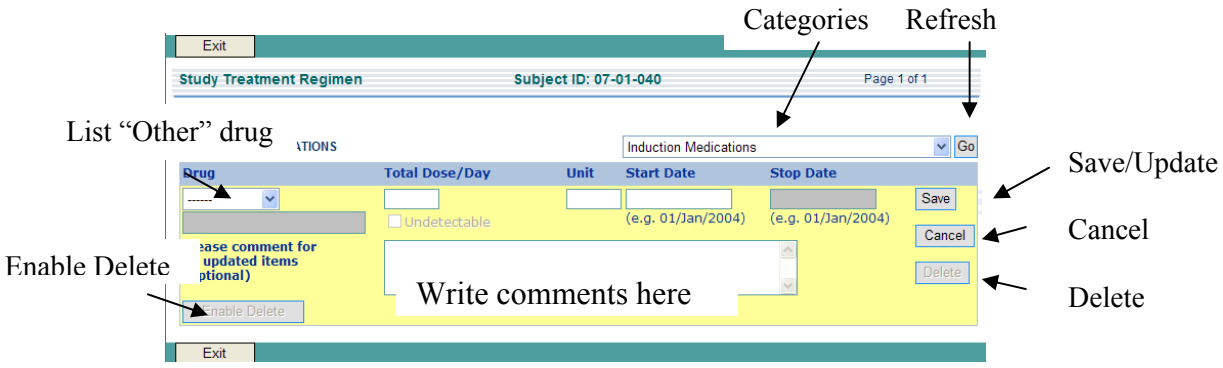
4.5.1 Catheter Introduction Method

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 infusion is the one that should be recorded.

4.6 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".

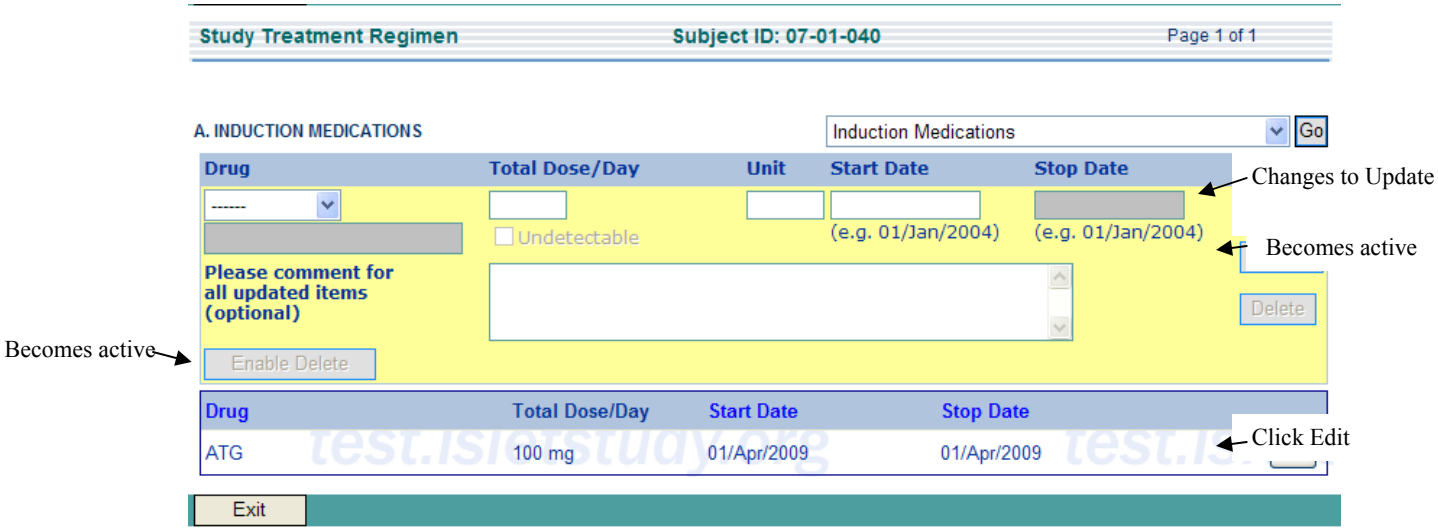
Delete – The delete button is not available until you click on the "Enable Delete" button. If you need to delete a drug, click on "Edit" in the row including the drug you wish to delete. Click on the "Enable Delete" button in the lower left of the screen. Then click on the "Delete" button.

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.

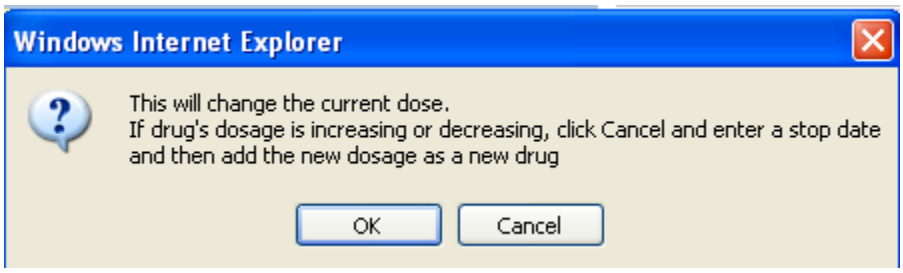
Correcting Errors: If you make a mistake in entering the dose or the date, or you wish to enter a stop date, click on the "Edit" button in the bottom right hand corner.



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.

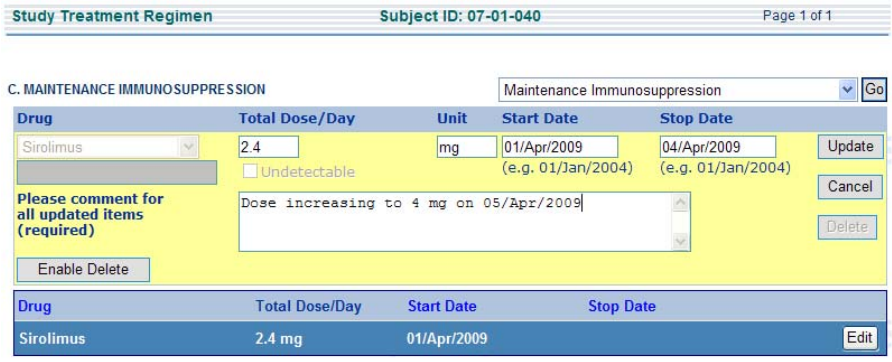
Enter stop date

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.

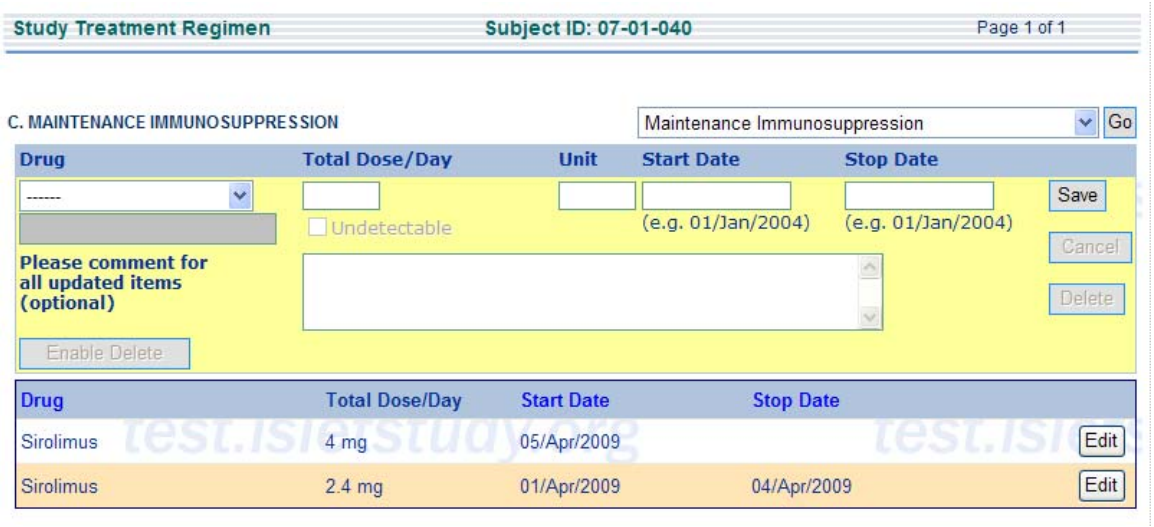
Click on "Update"



Click on "Go" to refresh screen

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

Click "Save".

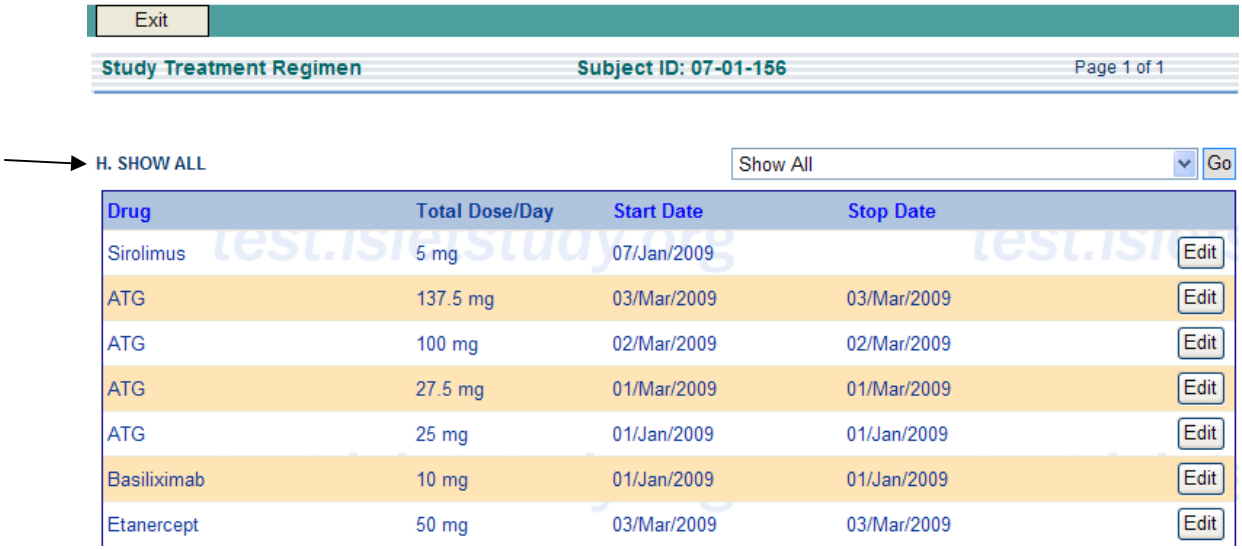


Trough Levels

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.

5. SAE/AE Reporting Procedures and Requirements

For specific information on reporting SAE s and AEs, please refer to the CIT Online Adverse Event Reporting System User's Manual.

5.1 Back-up AE/SAE Reporting Procedures

In the event of failure of the online AE 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 on-line 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 10) and fax it to the 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 Medical Reviewer 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.

5.2 Adverse Event Reporting of Chronic Conditions

5.2.1 Definitions

- 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.
- Worsening/exacerbation of a chronic condition: A change from non-serious to serious, or an increase in severity grade, according to the CIT-TCAE.

5.2.2 Initial Adverse Event Reporting

A new AE should be reported when:

- 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
- The subject experiences a worsening or exacerbation of a chronic condition (for example, a patient previously well-controlled hypertension has a hypertensive crisis).

5.2.3 Follow-up Reporting

Changes in seriousness:

- 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.
- Once an event is considered serious, it should remain as serious until resolution.

Changes in severity:

- The severity grade (using the CIT-TCAE) recorded on the AE eCRF should reflect the highest severity experienced during the course of the event.
- 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.

5.2.4 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:

- 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 illness persists for three months or more.

6. Reduced Follow-Up and Study Termination

6.1 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 (365 days post-final transplant). Study coordinators must emphasize to subjects who are 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. Study coordinators 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 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.**

Complete the following assessments at the intervals (± 7 days) relative to the day the subject discontinued treatment: Assess SAEs and hypoglycemic events: q1 month. If subject does not come to the study site for the visit, attempt to obtain information via a phone contact.

Additionally, the subject should return to the clinic for a 365 day post-initial transplant visit. Several assessments will be conducted at this visit: Alloantibody, HbA1c, MMTT, 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 365-day visit and for the 365-day post initial transplant visit (if the subject will not be seen at the clinic for this visit). 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.

Subjects on reduced follow-up who were withdrawn from the study prematurely due to graft failure will not receive additional study treatment in CIT-01. Therefore, such subjects may enroll in a graft failure follow-up study, if one is available.

6.2 Study Termination

If a subject is terminated from a CIT islet-alone study for reasons of ineligibility during screening or while on WL/BL, and s/he has an "open" (unsubmitted) *Screening Eligibility* or *Randomization 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.

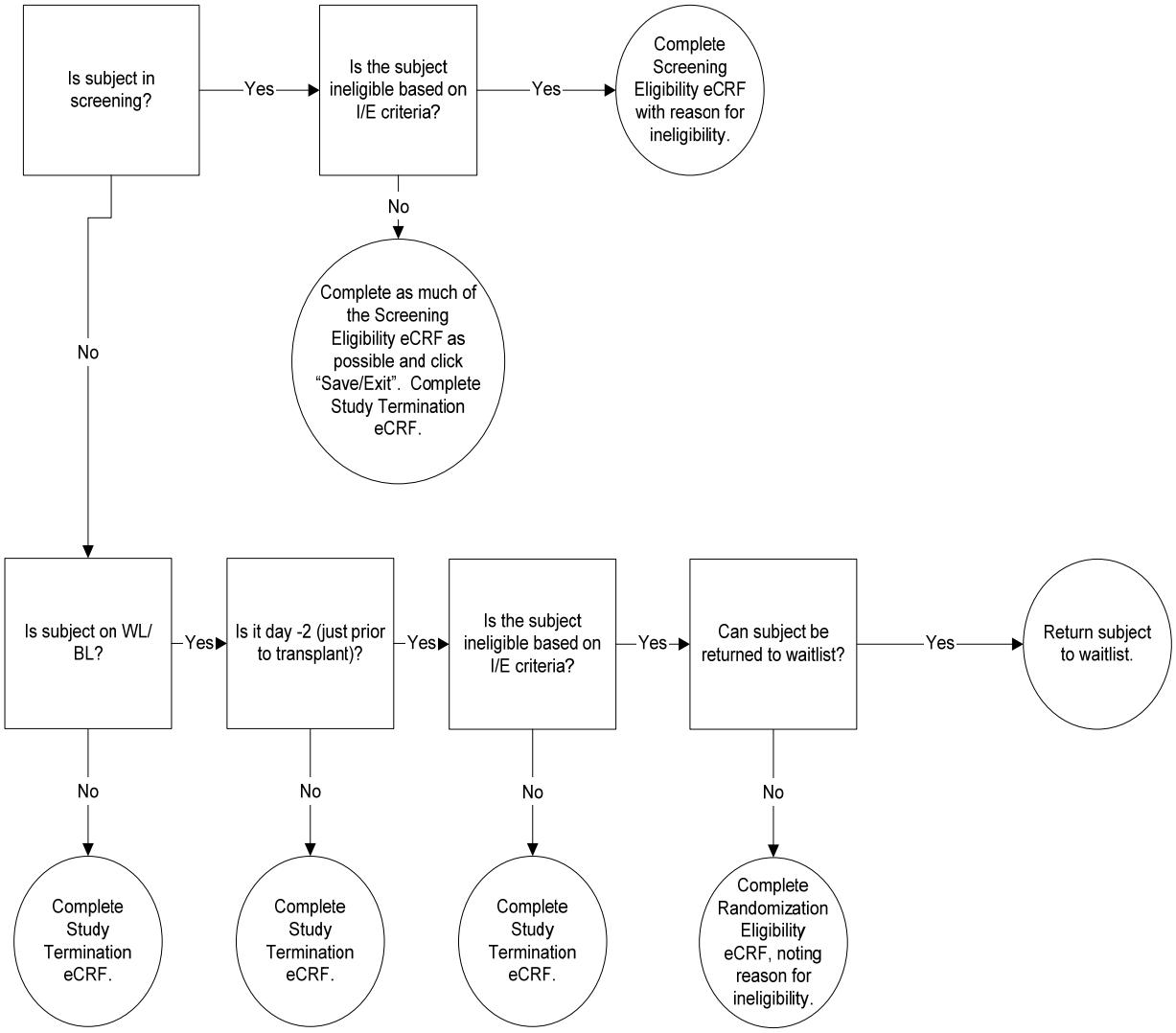
If a subject is terminated from a CIT islet-alone study for other reasons (not related to eligibility) during screening, the coordinator should complete as much of the subject's *Screening Eligibility* eCRF as possible based on data collected up to the point of termination. If some questions on this 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. 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 a CIT islet-alone study for reasons that are not related to eligibility during WL/BL, the coordinator should simply complete the Study Termination eCRF. The *Randomization 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 randomize him/her.

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

If a subject is terminated from the study and subsequently is able to re-enroll (based eligibility) or wishes to re-enroll (and the PI agrees that t he 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.

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



7. Study Drug Accountability

7.1 Investigational Drug Accountability

Each site is required to keep a record of receipts and dispositions of all investigational drugs received for the CIT-01 study. This should be done using a Drug Accountability Record (Appendix 9).

This form is designed to be used for maintaining perpetual inventories. Each time a drug is received, dispensed, or destroyed an appropriate entry must be documented on the Drug Accountability Record for the investigational drug. The inventory balance documented on the form should match the actual investigational drug inventory on hand at all times. When the recorded balance and actual inventory are not equal, an investigation should be conducted and the results of the investigation should be provided on the Drug Accountability Record.

TikoMed oversees the activities of the manufacturing of the LMW-DS and is the drug manufacturer. The active ingredient is produced by pK Chemicals, a Danish company, who then distributes the material to the

Swedish National Pharmacy (Apoteket AB. Produktion & Laboratorier (APL Umea, Sweden) for filling, labeling, and QA testing for activity and purity. The study drug is stored at APL Umea who will distribute to the Swedish (Apoteket AB) and Norwegian (Sykehusapotekene) local hospital pharmacies. The three enrolling centers will be ordering study drug from these local pharmacies (Uppsala, Huddinge, and Oslo, respectively).

The LMW-DS (20mg/mL) will be provided in 50 mL glass vials with rubber stoppers. APL: Umea is responsible for the storage, labeling, and the release of the vials to the Swedish (Apoteket) and Norwegian (Sykehusapotekene) local hospital pharmacies. APL Umea will distribute 60 vials of LMW-DS to each of the local pharmacies (Uppsala, Huddinge, and Oslo) with CIT-01 enrolling centers. The remaining vials will be stored with the manufacturer (APL Umea) until additional study drug is needed at the local hospital pharmacies.

The drug accountability records must be retained for the duration of the study. These records shall be made available upon request for inspection and copying by the sponsor's authorized representative or monitor.

7.2 Storage

When a drug order is received from the local hospital pharmacy, the shipment should be inspected as soon as possible. Carefully check items against the packing slip, noting container sizes, quantities, and lot numbers. The local hospital pharmacy should be notified immediately if there are any discrepancies.

Place study drugs in the appropriate storage area. This area must be kept separate from routine pharmacy stock, and should have limited access. The vials should be stored in a separate bin, labeled with the study identification and site PI name.

7.3 Dispensing

The local hospital pharmacies will dispense drug to the Transplant Wards. The Transplant Wards will re-order through the local hospital pharmacy, and the local hospital pharmacy will re-order through APL Umea.

The following guidelines are to be followed when dispensing investigational study drugs:

1. Establish and maintain a mechanism to ensure that study products are dispensed in a manner appropriate for the institution.
2. Establish a method to verify that a valid, signed consent form has been received from the subject before dispensing the study drug.
3. Prepare and dispense the investigational drug products in accordance with the EC approved protocol.
4. Instruct the appropriate clinic personnel on the correct use and dispensing of the investigational drug.

7.4 Study Drug Administration

The study drug, Low Molecular Weight Sulfated Dextran (LMW-DS) will be administered to those subjects randomized to the experimental arm to target an aPTT of 150 +/- 10 seconds. The LMW-DS will be administered according to the algorithm described in Appendix 8. Initially, each subject will receive a bolus of LMW-DS intraportally of 1.5 mg/kg body weight at 0 hour. From 0-20 minutes, each subject will receive an infusion of LMW-DS of 3 mg/kg added to the islet infusion and administered intraportally. From 20-32 minutes, each subject will receive an infusion of 0.7 mg/kg of LMW-DS added to the islet infusion "washing solution" and administered intraportally. At 32 minutes, a continuous intravenous infusion will be initiated based on the subject's aPTT at 20 minutes and adjusted to achieve the target aPTT of 150 +/- 10 seconds.

Subjects will receive LMW-DS for 5 hours with close monitoring of aPTT levels. Please see the CIT 01 website at http://www.isletstudy.org/ for worksheets to calculate the exact volumes of study drug and infusion rates for individual subjects based on body weight.

7.5 Study Drug Destruction Procedures

Unused, partially used and empty Low Molecular Weight Sulfated Dextran (LMW-DS) vials are to be destroyed by the local hospital pharmacy, according to standard operating procedures. Final disposition of the drug to the local hospital pharmacy should be documented in the Drug Accountability Record.

NOTE: It is mandatory to retain the LMW-DS partially used or empty vials after administered to a participant for a period of at least 1 week, prior to dispensing them to the local hospital pharmacy for destruction.

8. Study Supplies and Accountability

Each clinical site will receive shipments of One Touch Ultra Meters (LifeScan) from Lifescan, Inc (European Distributor) 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 (Appendix 11) in their study materials binder. Additional meters may be ordered by contacting the DCC protocol coordinator. If a glucometer is non-functional, contact the DCC protocol coordinator for return procedures..

Each clinical site will also receive shipments of CGMS (Medtronics) from Fisher Clinical Services including monitors and sensors. Each enrolled subject will be fitted with the monitor and sensor at baseline, day 75, day 365 and Year 1 for 72-84 hours of continuous glucose monitoring. The data will be downloaded by the sites from the monitors and then uploaded to the DCC (see Section 3.8.3). 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 12) in their study materials binder. Additional supplies may be ordered by contacting the DCC Protocol Coordinator. Replacement sensors that are expired will be handled by the DCC. If a meter is returned to the site it should be cleaned per institutional standards, tested for quality control, 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.

Appendix 1: DSMB Charter

NATIONAL INSTITUTE OF DIABETES, DIGESTIVE, AND KIDNEY DISEASES
DATA AND SAFETY MONITORING BOARD CHARTER

The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to NIDDK to monitor patient safety and evaluate the efficacy of the intervention. Dr. Korsgren, Uppsala University Hospital, Sweden is conducting a clinical trial entitled, "Open Randomized Multi-Center Study to Evaluate Safety and Efficacy of Low Molecular Weight Sulfated Dextran in Islet Transplantation," with the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK).

DSMB RESPONSIBILITIES

The initial responsibility of the DSMB will be to approve the initiation of this clinical trial. After this approval and at periodic intervals (to be determined) during the course of the trial, the DSMB responsibilities are to:

- review 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 and NIAID, the PI, and, if required, to the Food and Drug Administration (FDA) and the Ethics Committees (EC)/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 and NIAID by commenting on any problems with study conduct, enrollment, and sample size and/or data collection.

MEMBERSHIP

The DSMB will consist of at least five members. Three members will constitute a quorum. Membership consists of persons completely independent of the investigators who have no financial, scientific, or other conflict of interest with the trial. Collaborators or associates of Dr. Korsgren are not eligible to serve on the DSMB. Written documentation attesting to absence of conflict of interest is required. The DSMB includes experts in or representatives of the fields of:

- relevant clinical expertise,
- clinical trial methodology, and
- bio-statistics.

The NIDDK DSMB Chair has been selected by NIDDK. The Chair is responsible for overseeing the meetings, developing the agenda in consultation with the NIDDK Program Official. The chair is the contact person for the DSMB.

A Safety Officer will be identified 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. A NIDDK Official(s) will be present at every meeting. Meetings shall be closed to the public because discussions may address confidential patient data. Meetings are attended, when appropriate, by the principal investigator and members of his/her staff. 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 patient safety arise.

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 and NIAID staff, but should always include the study biostatistician. Issues discussed at open sessions will include conduct and progress of the study, including patient accrual, compliance with protocol, and problems encountered. Patient-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 by part or all of the closed session (e.g., study statistician, NIDDK or NIAID 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 the 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 or NIAID 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 patients and helps protect the study from bias in patient 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: Back-up Randomization Reporting Form

Fax to +1-319-335-6535

Attention: Traci Ripperda

Site Code: ___ ___ **Site Name_____**

Screening Number: **01___ - __ __ - __ __ __**

Envelope Sequence Number: _____

Date Envelope Opened: __ __/__ __ __/__ __ __ __

Local Time Envelope Opened: __ __:__ __

Treatment Assignment (*circle one*): **Study Arm 1: LMW-DS**
Study Arm 2: State of the Art

Delegated Responsible Site Personnel Initials: __ __ __

Appendix 3: Demographics Source Document

Subject Name: _____

Screening ID Number: 01___ - ___ ___ - ___ ___ ___

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 4: Clarke Survey

Hypoglycemia Clinical Symptom Questionnaire

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

INSTRUCTIONS: 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 experiences 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

Hypoglycemia Clinical Symptom Questionnaire (Clarke Survey Scoring Guide)

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

INSTRUCTIONS: Please answer the following questions to the best of your ability.

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 5: Blood Sugar Record/HYPO Log 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	12AM	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12PM	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	*basal*
Blood Sugar																									
Insulin Units																									*bolus*
Meal Code																									

Date: Insulin

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

Date: Insulin

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

Date: Insulin

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

Date: Insulin

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

Date: Insulin

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

Date: Insulin

Time	12AM	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12PM	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	*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	12AM	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12PM	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	*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				Total Insulin		
Time	12AM	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12PM	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	*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				Total Insulin		
Time	12AM	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12PM	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	*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				Total Insulin		
Time	12AM	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12PM	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	*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				Total Insulin		
Time	12AM	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12PM	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	*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				Total Insulin		
Time	12AM	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12PM	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	*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				Total Insulin		
Time	12AM	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12PM	1:00	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	*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.

  - **Each day starts at midnight (12:00 AM) exactly and endst at 1 minute before midnight (11:59 PM).**
  - 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 6: 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 7: Full HYPO Score Source Document

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

Full HYPO Score Source Document

Questions for Calculation of Full HYPO Score
(Visits 01, 02 [yearly] 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 8: Administration of LMW-DS in order to target an APTT of 150±10s (Version 1.3)

A) 0 min Bolus dose 1.5 mg*kg^{-1}
(B) 0 - 20 min Infusion 3 mg*kg^{-1} (Islet infusion medium)
(C) 20 - 32 min Infusion 0.7 mg*kg^{-1} (Washing Solution)

The maximum APTT at either 20 or 22 min* (**$APTT_{20min}$**) is used to calculate the infusion rate. The infusion rates are based on the following formulas:

(D) 32 – 60 min
If **APTT20min** is ≥234s then: 0.5mg*h^{-1}*kg^{-1}* body $weight_{kg}$ =…… (mg/h)
If **APTT20min** is ≥160 (& <234s) then: (4.7- 0.05 * (**APTT20min** -150)) mg*h^{-1}*kg^{-1} * body $weight_{kg}$: =…… (mg/h)
If **APTT20min** is <160 then: high concentration infusion for less than 1 minute, according to:
(160-**APTT20min**) * 0.05 mg*kg^{-1} * body $weight_{kg}$ =…… (mg)#
Followed by infusion of (4.7- 0.05 * (**APTT20min** -150)) mg*h^{-1}*kg^{-1}* body $weight_{kg}$ =…… (mg/h)

(E) 60 – 100 min (2.2- 0.0027 * (**APTT20 min** -150)) mg*h^{-1}*kg^{-1}* body $weight_{kg}$ =…… (mg/h)

(F) 100 - 140 min (1.9- 0.007 * (**APTT20 min** -150)) mg*h^{-1}*kg^{-1}* body $weight_{kg}$ =…… (mg/h)

(G) 140 - 332 min (1.7- 0.004 * (**APTT20 min** -150)) mg*h^{-1}*kg^{-1}* body $weight_{kg}$ =…… (mg/h)

***If APTT at 20 or 22 min is not available the infusion rate for APTT20min 175s should be installed at 32 min.**
This infusion rate can be maintained for maximum 10 min.
When the APTT value is available the infusion rate should be immediately adjusted according to the calculator.
#Note: Give maximal 3 mg/kg (correspond to $APTT_{20min}$ = 100s)

APTT should be measured at 10, 20, 22, 50, 90, 130 min and every 60 min thereafter (more often if necessary). Target levels are:

At	50 min	150-175s
	90 min	141-159s
	130 min	135-150s

If APTT is outside these ranges at the specified time points the infusion rate should be adjusted by 10-20% (minus if too high; plus if too low)

Worksheets for calculation of exact volumes and infusion rates for individual patients are available on the CIT-01 website (http://www.isletstudy.org).

Appendix 9: DRUG ACCOUNTABILITY RECORD

PROTOCOL CIT-01
RESEARCH PHARMACY BINDER

Name of Institution	**IND#:**
Drug Name, Dose Form and Strength: **Low Molecular Weight Sulfated Dextran (LMW-DS)**	
Protocol Title: **Open Randomized Multi-Center Study To Evaluate Safety and Efficacy of Low Molecular Weight Sulfated Dextran in Islet Transplantation**	
Principal Investigator:	

DATE RECEIVED	QUANTITY RECEIVED (# Vials)	QUANTITY DISPENSED (# Vials)	DATE DISPENSED	QUANTITY DESTROYED	SUBJECT STUDY ID NUMBER	BALANCE FORWARD (# vials)	LOT NO.	Recorder's initials

NOTE: All vials should be retained for a period of 1 week after the infusion of the LMW-DS to each participant, and then destroyed according to your institutions procedure

Appendix 10: Back-Up Manual Adverse Event Reporting Form

CIT-01 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. O O 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
Safety and Efficacy of Low Molecular Weight Dextran Sulfate (LMW-DS) in Islet Transplantation

Version 4.0
24/Aug/2009

CIT-01 ADVERSE EVENT

Subject ID ___ ___ -___ ___ - ___ ___ ___ Page 2 of 5

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)
O Mild/Grade I
O Moderate/Grade II
O Severe/Grade III
O Life-threatening/Grade IV
O Death/Grade V
(If question 9 is Death/Grade V, then go to question 10)

10. Was/will an autopsy be performed? (select one)
O No
O Yes _____ Please provide a de-identified copy to the DCC
O Unknown

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

Subject ID ___ ___ -___ ___ - ___ ___ ___ Page 3 of 5

Report Number _____

	No	Yes	
12.	O	O	Has the subject ever received the investigational drug, LMW-DS?

a. Relationship to LMW-DS
- O Definite
- O Probable
- O Possible
- O Unlikely
- O Unrelated, Explain: [ ]

b. Action taken regarding LMW-DS
- O None
- O Dose reduced
- O Interrupted
- O Discontinued
- O Dose increased

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

a. Relationship to islet transplant procedure
- O Definite
- O Probable
- O Possible
- O Unlikely
- O Unrelated, Explain: [ ]

b. Action taken regarding islet transplant procedure
- O Infusion not started
- O None
- O Interrupted but completed
- O Prematurely terminated

	No	Yes	
14.	O	O	Has the subject ever received immunosuppression and/or infection prophylaxis?

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

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

CIT-01 ADVERSE EVENT

Subject ID ___ ___ - ___ ___ - ___ ___ ___

Report Number _____

B. Suspect Medication(s)

	Suspect Medication 1	Suspect Medication 2	Suspect Medication 3
1. Name	Low Molecular Weight Sulfated Dextran	Islet Transplantation ☐ Islet Product (check if ever received islets) ☐ Transplant Procedure (check if ever had transplant procedure initiated)	Immunosuppression and infection prophylaxis
2. Total Dose	i	ii	
3. Therapy Dates (if unknown, give best estimate)	Introduction Date __/___/_____ Date of last Dose __/___/_____ (dd/mmm/yyyy)	Date of most recent Islet Transplantation __/___/_____ (dd/mmm/yyyy)	
4. Diagnosis for use	Islet Transplant/Immunosuppression	Type I Diabetes Mellitus	Islet Transplant/Immunosuppression
5. Event abated after use stopped or dose reduced?	i. ○ No ○ Yes ○ Doesn't apply	ii. ○ No ○ Yes ○ Doesn't apply	iii. ○ No ○ Yes ○ Doesn't apply
6. Event reappeared after reintroduction?	i. ○ No ○ Yes ○ Doesn't apply	ii. ○ No ○ Yes ○ Doesn't apply	iii. ○ No ○ Yes ○ Doesn't apply
7. Lot Number	i.	ii.	
8. Expiration date (if known)	i. __/___/_____ (dd/mmm/yyyy)	N/A	

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.

Appendix 11: Accountability Log for Glucometers

GLUCOMETER ACCOUNTABILITY LOG
STUDY MATERIALS BINDER

Name of Institution	**IND#: N/A**
Protocol Title: **Open Randomized Multi-Center Study To Evaluate Safety and Efficacy of Low Molecular Weight Sulfated Dextran in Islet Transplantation**	
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

Appendix 12: Accountability Log for CGMS

CGMS ACCOUNTABILITY LOG
STUDY MATERIALS BINDER

Name of Institution	**IND#:** N/A
Protocol Title: Open Randomized Multi-Center Study To Evaluate Safety and Efficacy of Low Molecular Weight Sulfated Dextran in Islet Transplantation	
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

Appendix 13: CIT-01 inclusion/exclusion criteria checklist and source documentation location.
The greyed-out criteria listed below require additional source documentation.

CIT-01 INCLUSION CRITERIA		
Criterion Met?	**Criterion**	**Location**
No ☐ Yes ☐	1. Patients between 18 to 65 years of age.	medical record
No ☐ Yes ☐	2. Subjects who are able to provide written informed consent and comply with the procedures of the study protocol.	
No ☐ Yes ☐	3. Clinical history compatible with T1D with onset of disease at < 40 years of age, insulin-dependence for ≥ 5 years at the time of enrollment, and a sum of patient age and insulin dependent diabetes duration of ≥ 28.	
No ☐ Yes ☐	4. Absent stimulated c-peptide <0.3ng/mL [0.099 nmol/L] in response to a mixed meal tolerance test (MMTT; Boost® 6 mL/kg body weight 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 the start of consumption.	Central lab results
No ☐ Yes ☐	5. Involvement in intensive diabetes management defined as 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. 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.	
No ☐ Yes ☐	6. At least one episode of severe hypoglycemia, 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, in the 12 months prior to study enrollment.	

CIT-01 INCLUSION CRITERIA		
Criterion Met?	**Criterion**	**Location**
No ☐ Yes ☐	7. Reduced awareness of hypoglycemia as defined by a Clarke score of 4 or more and a HYPO score greater than or equal to the 90th percentile (1047) during the screening period and within the last 6 months prior to randomization; **OR** Marked glycemic lability characterized by wide swings in blood glucose despite optimal diabetes therapy and defined by an LI score greater than or equal to the 90th percentile (433 mmol/L^2/h·wk^{-1}) during the screening period and within the last 6 months prior to randomization; **OR** A composite of a Clarke score of 3 or more and a HYPO score greater than or equal to the 75th percentile (423) and a LI greater than of equal to the 75th percentile (329) during the screening period and within the last 6 months prior to randomization.	Screenshots of metabolic and Clarke score calculations

CIT-01 EXCLUSION CRITERIA		
Criterion Met?	**Criterion**	**Location**
No ☐ Yes ☐	1. Known IgE mediated allergy to antibiotics and antifungal medications (ciprofloxacin, gentamycin, and amfotericin B) used in the culture medium.	
No ☐ Yes ☐	2. Known hypersensitivity to dextran.	
No ☐ Yes ☐	3. Body mass index (BMI) >30 kg/m^2.	medical record
No ☐ Yes ☐	4. Insulin requirement of >1.0 U/kg/day.	medical record
No ☐ Yes ☐	5. HbA1c >10%.	Central Lab results
No ☐ Yes ☐	6. Untreated proliferative diabetic retinopathy.	medical record
No ☐ Yes ☐	7. Blood Pressure: SBP >160 mmHg or DBP >100 mmHg.	medical record
No ☐ Yes ☐	8. Measured glomerular filtration rate using 51Cr-EDTA, 99technetium-DPTA, or iohexol <80 mL/min/1.73m^2. The absolute (raw) GFR value will be used for subjects with body surface areas >1.73 m^2.	medical record
No ☐ Yes ☐	9. Presence or history of macroalbuminuria (>300mg/g creatinine).	medical record
No ☐ Yes ☐	10. Presence or history of panel-reactive anti-HLA antibodies >80% by flow cytometry. Subjects with panel reactive anti-HLA antibodies above background but ≤80%, can be included if the antigen specificity of the antibodies can be determined for future avoidance; however, if the antigen specificity of the antibodies cannot be determined they will be excluded.	Central Lab results
No ☐ Yes ☐	11. 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.	medical record
No ☐ Yes ☐	12. Active infection including hepatitis B, hepatitis C, HIV.	medical record
No ☐ Yes ☐	13. Negative screen for Epstein-Barr Virus (EBV) by IgG determination.	medial record
No ☐ Yes ☐	14. Any history of malignancy except for completely resected squamous or basal cell carcinoma of the skin.	
No ☐ Yes ☐	15. Known active alcohol or substance abuse.	
No ☐ Yes ☐	16. Baseline Hb below the lower limits of normal at the local laboratory; lymphopenia (<1,000/μL), neutropenia (<1,500/μL), or thrombocytopenia (platelets <100,000/μL).	medical record
No ☐ Yes ☐	17. Homocygotic Activated Protein C Resistance (APC-R)	medical record
No ☐ Yes ☐	18. History of hypercoagulability disorder or coagulopathy or an international normalized ratio (INR) >1.5.	

CIT-01 EXCLUSION CRITERIA		
Criterion Met?	**Criterion**	**Location**
No ☐ Yes ☐	19. Known history of severe co-existing cardiac disease, characterized by any one of these conditions: a) recent myocardial infarction (within past 6 months). b) evidence of ischemia on functional cardiac exam within the last year. c) left ventricular ejection fraction <30%.	medical record
No ☐ Yes ☐	20. Consistently abnormal liver function tests at the time of study entry. SGOT (AST), SGPT (ALT), Alk Phos or total bilirubin, with values >1.5 times normal upper limits on two consecutive measurements >2 weeks apart.	medical record
No ☐ Yes ☐	21. Acute or chronic pancreatitis.	
No ☐ Yes ☐	22. Patients with active peptic ulcer disease, symptomatic gallstones or a history of portal hypertension.	
No ☐ Yes ☐	23. Severe unremitting diarrhea, vomiting or other gastrointestinal disorders potentially interfering with the ability to absorb oral medications.	
No ☐ Yes ☐	24. Receiving treatment for a medical condition requiring chronic use of systemic steroids, except for the use of $\leq$ 5 mg prednisone daily, or an equivalent dose of hydrocortisone, for physiological replacement.	
No ☐ Yes ☐	25. Treatment with any anti-diabetic medication other than insulin within 4 weeks of enrollment.	
No ☐ Yes ☐	26. Use of any investigational agents within 4 weeks of enrollment.	
No ☐ Yes ☐	27. Administration of live attenuated vaccine(s) within 2 months of enrollment.	
No ☐ Yes ☐	28. Patients with any condition or any circumstance that in the opinion of the investigator would make it unsafe to undergo an islet transplant.	
No ☐ Yes ☐	29. Treatment with any immunosuppressive regimen at the time of enrollment.	
No ☐ Yes ☐	30. A previous islet transplant.	
No ☐ Yes ☐	31. A previous pancreas transplant, unless the graft failed within the first week due to thrombosis, followed by pancreatectomy and the transplant occurred more than 6 months prior to enrollment.	

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

_____ Date _____

Signature of PI or designee (listed on IOR)

Appendix 14: CIT-01 – Guide to Deviation Classifications

Major Deviations: Notify the NIH Project Manager immediately phone or email. You will also need to complete the Protocol Deviation eCRF, and submit to DCC.

Non-Major deviations are logged on your monitoring report.

Category	Major Deviations (Violations)	Minor Deviations
Informed Consent	➢ Consent not signed ➢ Wrong version of consent , i.e. not EC or NIH approved ➢ Consent not signed at appropriate time e.g. enrollment consent must be signed before screening and randomization consent immediately after randomization. ➢ PI did not document his/her involvement of informed consent process in the medical record	
Inclusion/exclusion criteria	➢ Eligibility information is measurable or verifiable and documentation does not exist ➢ Subject enrolled, but does not meet inclusion/exclusion criteria	➢ Non-metabolic screening assessment windows exceeded
Study Medications • LMW-DS or heparin • Induction drug, polycolonal IgG antibody Rabbit Antithymocyte Globulin® • Cell Proliferation Inhibitor (CellCept®, Rapamune®) • Calcineurin Inhibitor (Prograf®, Sandimmune® or Neoral®) • Monoclonal Antibody IL-2 Receptor Blocker (Simulect®) basiliximab • TNF Inhibitor (Enbrel®)	➢ Study drugs not administered per protocol	➢ Pre-medication not administered per protocol

Category	Major Deviations (Violations)	Minor Deviations
Concomitant /ProphylacticMedications (Prophylaxis for infection, pneumocystis jiroveci pneumonia, CMV, and/or hypersensitivity)	➢ Prophylactic Medications (also considered study drugs) not administered (no clinical rationale for not administering)	➢ Dosing of prophylactic mediations not according to protocol (doses adjusted due to a clinical rationale do not constitute a deviation)
Prohibited Medication (See Section 5.8)	➢ Medication prohibited in protocol were given	
Safety,Endpoint & Metabolic Assessments	➢ For any day 75 or 1 year post initial or final transplant (visit number 10, 12 or Y1) endpoint or safety assessments not done or done outside of the visit window ➢ HYPO events/BSR inadequate for calculations of eligibility or primary endpoint ➢	➢ 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. ➢ For all visits, **except** day 75 or 1 year post initial or final transplant (visit number 10,12 or Y1) • Any local lab assessment not done or done outside of the window (refer to SOE) • Any general assessment not done or done outside of the window (refer to SOE)Any central lab assessment not done or done outside of the window (refer to SOE)
Adverse Event Reporting	➢ Insufficient AE collection, Grade 3 and higher not reported ➢ Failure to report SAE within 24 hours (of site becoming aware of SAE)	➢ Grade 1 and 2 AEs not entered into eCRF, though documented in the patient record
Clinical Labs & Assessments	➢ Labs affecting safety endpoints not completed	➢ Physical exam not done at any post-transplant visit where it is required

Category	Major Deviations (Violations)	Minor Deviations
		➢ 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 is due
Mechanistic or Archived Sample Collection	➢ Samples drawn without subject consent	➢ Samples not drawn due to blood volume issues

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 02- WL/BL)	
	Not Done	Out of Window	Not Done	Out of Window◆
General Assessments				
Medical and diabetes history	Major			
Retinopathy exam (screening)	Minor	Minor		Minor◆
Physical exam	Minor	Minor		Major
Vitals	Minor	Minor		Minor◆
QOL	Major	Major	Minor	Minor◆
Chest x-ray	Major	Major		Minor◆
Abdominal US	Major	Major		Minor◆
ECG	Major	Major		Minor◆
Myocardial Scintigram	Major			
Conduction Velocity & RR intervals	Major			
Local Lab Assessments				
CBC	Major	Major		Minor◆
Chemistry	Minor	Minor		Minor◆
Lipids	Major	Minor		

Liver Enzymes (ALT, AST)	Major	Minor	Major	Minor◆
Pregnancy Test	Major		Major	Major
Serology	Major	Major	Major	Major
CMV IgG/IgM	Major			
CMV/EBV by PCR			Major	
Coagulation	Major	Major	Major	Major
GFR	Major		Major	Major
Blood type	Major			
HLA	Major			
Crossmatch			Major	Minor◆
HIV, Hepatitis B, Hepatitis C	Major	Major	Major	Major
Central Lab/Metabolic Assmts				
HbA1c	Major			Minor◆
MMTT	Major			
FSIGT			Minor	Minor
Local Metabolic Assmts				
CGMS	Major	Major	Major	Major
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		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.

Appendix 15: HYPO Assessment Sheet

Patient 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 16:
Source Tool: Eligibility for Second Transplant
CIT01 Protocol Version 7.0

1. If the subject has partial graft function, have the day 75 assessments been completed?
( )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. Has the subject reached 8 months post-first initial islet infusion?
( )Yes ( )No *If 'Yes', subject is not eligible for a 2nd 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 has Graft Failure (need SC or NNSC approval) or Partial Graft Function.	
	2. Subject has been compliant with study monitoring and prescribed immunosuppressive therapy	
	3. No evidence of a serious and life-threatening infection, adverse event, or other condition that precludes attempting an intraportal injection or continuation of the post-transplant treatment regimen.	
	4. No evidence of post-transplant lymphoproliferative disorder (PTLD).	
	5. No evidence of progressive renal dysfunction, with blood creatinine rising above 2.0 mg/dL (177 umol/L) with calcineurin inhibitor trough levels within maintenance levels.	
	6. No evidence of hypersensitization, allergic responses, or other potentially serious drug reactions to medications required by the protocol.	
	7. It has been < 8 months since the first islet transplant. (For example if the first transplant was on 1/1 then the second transplant must be done by 9/1.)	
	8. Absence of 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 17: Source Tool: Eligibility for Third Transplant

CIT01 Protocol Version 7.0

1. Does the subject have partial graft function?
   ( )Yes ( )No ( )N/A *If 'No', subject is not eligible for a third transplant.*

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

3. 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. The subject remains without full islet graft function.	
	2. There is evidence of partial graft function (C-peptide ≥ 0.1 nmol/L (≥0.3ng/mL).	
	3. No evidence of post-transplant lymphoproliferative disorder (PTLD).	
	4. The CIT Principal Investigator and Site Principal Investigators have determined that there were no relevant protocol deviations at the site.	
	5. The subject has been compliant with study monitoring and prescribed immunosuppressive therapy.	
	6. 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.	
	7. No evidence of progressive renal dysfunction, with blood creatinine rising above 2.0 mg/dL (177 umol/L).	
	8. No evidence of hypersensitization, allergic responses, or other potentially serious drug reactions to medications required by the protocol.	
	9. No evidence of abnormal liver ultrasound and LFTs within 1.5 ULN range.	
	10. The 28 day (± 3 days) visit following the second transplant has been completed.	
	11. Less than 8 months has passed after the first islet transplantation. (For example if the first transplant was on 1/1 then the third transplant must be done by 9/1.)	

Completed by: _____ date:_____

Investigator Signature: _____date:_____

Appendix 18: NON SUBJECT SPECIFIC MAJOR or MINOR DEVIATIONS:

Sites should send an e-mail to the DCC coordinator and NIH project Manager with information describing the deviation and the corrective action plan. The description should follow the format of the Major Deviation eCRF (Items 1 – 8) but be sent in a memo format:

To: <<DCC Protocol Coordinator>>
<<NIH Project Manager>>

From: <<Site Coordinator>>

Re: Non-clinical deviation

Description of the deviation: including date site became aware of deviation, who identified the protocol deviation, when did the protocol deviation occur and category of the deviation.

Description of how the deviation occurred

Describe the corrective plan to ensure that this deviation does not occur again

Appendix 19: Email from NNSC regarding 2nd Transplant after day 75

To: Nancy Bridges
V.K. Skaare
Yvonne Morrison
FROM: Protocol Chair of NNSC
Subject: Graft Failure NNSC

CIT-01 NNSC Meeting
Minutes and Decisions regarding graft failure

Attendance;

Study subject;

Presenting doctor;

Date of initial transplantation;

Date of suspected graft failure;

Date of confirmed graft failure;

Suspected cause of graft failure;

ATG Induction (yes/no):

Initial immunosuppression (at time of transplant);

Does the patient fulfill protocol criteria for a second transplant?

Decision on whether the patient may or may not be put on the waitlist for a second transplantation;

Signature (Protocol Chair)

Date

Cc: Olle Korsgren

Appendix 20: Email to DCC regarding decision of NNSC for 2nd Transplant after day 75

To: Dixie Ecklund
Traci Schwieger
Julie Qidwai

FROM: Nancy Bridges
V.K. Skaare
Yvonne Morrison

Subject: Graft Failure NNSC

The following document has been provided by the NNSC regarding subject xx-xx-xxx. The decision is to [place/not place] this subject on the waiting list for a second transplant.

CIT-01 NNSC Meeting
Minutes and Decisions regarding graft failure

Attendance;

Study subject;

Presenting doctor;

Date of initial transplantation;

Date of suspected graft failure;

Date of confirmed graft failure;

Suspected cause of graft failure;

ATG Induction (yes/no):

Initial immunosuppression (at time of transplant);

Does the patient fulfill protocol criteria for a second transplant?

Decision on whether the patient may or may not be put on the waitlist for a second transplantation;

Signature (Protocol Chair)
Date

Cc: Julia Goldstein
Deb Feddersen
Olle Korsgren
Omar El Mestikawy (TFS)