



COLLABORATIVE ISLET TRANSPLANT REGISTRY

MANUAL OF PROCEDURES

Version 3.0

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1.0 OVERVIEW

1.1. Overview of Collaborative Islet Transplant Registry

The mission of the Collaborative Islet Transplant Registry (CITR) is to expedite progress and promote safety in islet/beta cell transplantation through the collection, analysis, and communication of comprehensive and current data on all islet/beta cell transplants performed in North America, Europe and Australia.

The CITR Protocol outlines the background, purpose, organization and governance of the Registry; specifies site and participant eligibility; states the research goals and questions; and specifies the policies governing methods, data analysis, publication and presentation of results, confidentiality and protection of human subjects. This Manual of Operations details how the policies and procedures of the Registry are implemented. Through the contract between the NIDDK and the CITR Coordinating Center at the EMMES Corporation, Rockville, MD, the Manual of Operations carries the force of Protocol.

1.2. Registry By-laws

1.2.1. Purpose

The purpose of CITR shall be to engage in scientific activities and data collection endeavors including, but not limited to, gathering relevant data, promoting and fostering research and exchange, and diffusion of information and ideas relating to the use of islet/beta cells in transplants in support of treating and curing diabetes mellitus.

1.2.2. Operation

CITR is formed and funded by the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), with supplemental funding from the Juvenile Diabetes Research Foundation International (JDRFI). The EMMES Corporation is the core component of the Registry and will be known as the Coordinating Center, providing statistical support, data management services and organizational resources.

1.2.3. Meetings

There shall be an annual meeting of the CITR organization at a time and place to be determined by the Executive Committee. NIDDK or the SAC Chair may call additional meetings, if required.

1.2.4. Members

Participating transplant centers are centers that submit data on islet/beta cell transplants performed at their center, agree to use standard data collection instruments of the Registry, agree to have an initiation visit, agree to have data audits, and have center staff attend annual meetings. Each participating center must identify at least one Principal Investigator and one Transplant Coordinator/Data

Manager as contact persons for the Registry. These Participating Members may serve on committees of the Registry.

1.2.5. Officers

There shall be a Scientific Advisory Committee (SAC) appointed by the Coordinating Center in consultation with NIDDK. This committee will be comprised of a Chair and seven additional voting committee members. The NIDDK Project Officer and Registry's Coordinating Center Principal Investigator shall serve as permanent voting members of the SAC. The SAC shall conduct the business of the Registry in accordance with CITR-stated purposes.

The SAC Chair shall also preside at the study-wide annual meeting, be responsible for overseeing the final annual meeting agenda and serve as the official representative of the Organization.

There shall be an Executive Committee, comprised of the Project Officer from NIDDK, the SAC Chair and Medical Director, and the Director/Principal Investigator of the Coordinating Center. This Committee will oversee the routine operations of the CITR, answer Registry specific questions, and coordinate aspects of the Registry with the SAC.

1.2.6. Standing Committees

There shall be four standing Committees.

Compliance Committee: The Compliance Committee shall monitor compliance, identify barriers to consistent compliance with participant registration and follow-up, and suggest mechanisms to improve compliance. The Committee shall review the results of each data audit and recommend appropriate action based on the results of the audit.

Transplant Coordinators'/Data Managers' Committee: Each participating transplant center will identify at least one Registry Transplant Coordinator/Data Manager at their center for representation on this Committee. This person or persons will also participate in the Registry Coordinating Center's training and information sessions. The charge of this Committee shall be to provide logistical information to the SAC regarding the working of the Registry from the Coordinator's perspective.

Publications/Presentations Committee: The charge of this Committee is to develop and implement a clear and concise set of guidelines for the publication and presentation of data from the Registry. The Committee also shall be responsible for reviewing all proposals for primary and secondary analyses and publications. All results of the Committee will be recommended to the SAC for approval, disapproval, or modifications.

Data Elements Committee: This nine-person Committee consists of Principal Investigators, Islet Processing Investigators and at least one Transplant Coordinator/Data Manager nominated from the participating transplant centers.

The Committee is responsible for monitoring changes in the standard practice of islet transplantation, which includes islet isolation, purification, transplant technique, immunosuppressant medications, metabolic tests and recommending appropriate

modifications to the CITR data collection tools. The CITR Executive Committee will make a determination on the implementation of these recommendations.

In addition, the Scientific Advisory Committee or Executive Committee may, from time to time, appoint additional ad hoc committees as are necessary to carry out the purposes of CITR as stated above.

Membership and chairmanship of standing committees. A revised policy was approved by the Investigators at their 2007 Annual Meeting and subsequently approved by the Scientific Advisory Committee to comply with requirements set forth in the Agreement between the Coordinating Center and the funding agency. Starting in 2008, the Compliance Committee, Data Elements Committee and the Publications/Presentations committees shall each comprise nine members, each serving a three-year term. Each year thereafter, three members will rotate off of the committee and three new members will be elected from participating CITR centers. The nine rotating members of each Committee shall be elected by ballot by the participating transplant centers. Election shall require a plurality of votes cast by the voting due date. Each center will have one vote. No more than one representative from any one center can serve on any Committee during a term. For all committees, a chair will be elected every year to hold a one-year term of office. The chair must be someone who served on the committee during the previous year and is willing to remain on the committee ex-officio for the year following their term to provide assistance to the subsequent chair. With the chair's consent, the chair may be re-elected to another active term.

The Transplant Coordinators/Data Managers' Committee will comprise one representative from each activated CITR site. The Chair will be elected by the Committee to hold a one-year term of office. Election shall require a plurality of votes cast by the voting due date. The Chair will participate in all meetings and conference calls convened by the SAC from the time the Chair is elected.

1.2.7. Amendments

These By-laws may be amended at any annual meeting of the Organization. Amendments to the By-laws must be proposed in writing to the Scientific Advisory Committee Chair by any participating transplant center at least ninety days prior to the annual meeting of the CITR. The proposed amendments, together with the SAC's recommendations, shall be distributed by postal mail or electronically at least thirty days prior to the annual meeting at which the amendment is to be considered.

To be adopted, the amendment must receive the affirmative vote of a simple majority of the SAC.

1.3. CITR Data Collection

In order to capture the most relevant data, CITR defines and collects the most pertinent information on all islet transplant recipients who received their first islet infusion on January 1, 1999 or later, for both allografts and autografts.

1.4. Islet / Beta Cell Transplant Registration Procedures

Islet transplant recipients are registered in CITR by the transplant center once the patient has received an islet transplant and provided informed consent if alive at the

time their data is registered. If a patient has been evaluated and listed for an islet cell infusion, the center must wait until the infusion is performed before entering the patient in the Registry. Sites may register historical data for islet transplant recipients who have subsequently been lost to follow-up, if and only if their local IRB approves the abstraction of data from the medical record. In no event will any recipient be personally identified by means of personal identification, including but not limited to, name, address, telephone number, e-mail address, any medical, insurance or government-issued personal identifier. Detailed instructions for data entry are found in the CITR AdvantageEDCSM User's Guide.

1.5. Follow-up Procedures.

Each registered participant is followed at 30 days, six months and twelve months post first islet infusion. In addition, full data collection as specified in the study schedule (see CITR User's Guide in Secured Access section of www.CITRegistry.org) is conducted at six months and twelve months post last infusion and then yearly thereafter. The final follow-up schedule is based on the participants' last infusion.

2.0 PROJECT ORGANIZATION

CITR is financially supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDK) and has supplemental funding from the Juvenile Diabetes Research Foundation International (JDRFI.) The Coordinating Center at the EMMES Corporation provides statistical and data management support. The Executive Committee is responsible for operational oversight of CITR, while the Scientific Advisory Committee is responsible for the scientific integrity and policy advice to the sponsors regarding the Registry. The transplant centers participate through a letter of agreement with the Coordinating Center that promotes continuity of operations and facilitates effective communication and cooperation among the participating units. The Protocol shows the organizational structure of the Registry operations.

2.1. Transplant Centers

The success of a multi-center endeavor depends on the dedication and cooperation of the staff in all transplant centers to perform their tasks and responsibilities in an efficient, effective, and timely manner. Transplant centers are responsible for recruiting and registering islet transplant recipients and for collecting all clinical, laboratory, demographic and other data required by the Registry. The Principal Investigator (PI) representing the center is personally responsible for ensuring that Registry procedures are followed. Each transplant center is staffed, at a minimum, by a Principal Investigator (PI) and a Transplant Coordinator (TC)/Data Manager (DM). There may be additional staff designated as co-investigators, data managers or administrative personnel.

2.1.1. Functions of the Transplant Center Principal Investigator

The responsibilities of the designated Transplant Center PI are to:

- Vouch for the scientific validity of data on islet preparations, donors and islet transplant recipients entered into the Registry.
- Direct the activities of the CITR personnel in the transplant center.
- Coordinate the scientific and administrative operations of the transplant center.
- Ensure adherence by the CITR personnel to the procedures described in and required by the CITR Manual of Procedures and the AdvantageEDCSM User's Guide.
- Represent the transplant center at CITR meetings.
- Participate in CITR initiation visit and data audits by the Coordinating Center.
- Obtain CITR password to view the CITR web site and frequently review CITR activity.

2.1.2. Functions of the Transplant Coordinator / Data Manager

The Transplant Coordinator / Data Manager is responsible for supervising day-to-day operations in the transplant center and serves as primary contact for the Registry participants and for the Coordinating Center. The duties of the coordinator are to:

- Ensure that potential CITR participants receive appropriate information about the Registry, including the Informed Consent/Assent process and statements (if applicable).
- Ensure that potential participants have the opportunity to ask questions about CITR. Register participants via the Registry System (AdvantageEDCSM). Maintain a secure log of the correspondence between a transplant recipient by personal identifying information (name, address, telephone number, hospital chart number, health insurance identification number, etc), and the participant's CITR study number. Ensure that all documents transmitted to the Coordinating Center are identified only with the participant's CITR ID and no other personal identifying information. Provide for a system of secure, off-site archival of this log, maintained current at reasonable intervals (e.g., monthly).
- Maintain a current transplant center roster of Center personnel, address, telephone number(s) and notify the Coordinating Center of any changes.
- Maintain a file of correspondence with the Coordinating Center.
- Obtain necessary information about deceased participants (e.g., date and primary cause of death).
- Review updates of the CITR Manual of Procedures, AdvantageEDCSM System and User's Guide and Registry memorandums posted on the CITR Internet.
- Check completed data screens for accuracy and completeness.

- Ensure timely transmission of data to the Coordinating Center.
- Respond to data queries from the Coordinating Center in a timely fashion.
- Report irregularities or problems to the PI and to the Coordinating Center that can affect the quality of the data collected.
- Participate in CITR initiation visit and data audits by the Coordinating Center.
- Represent the transplant center at CITR meetings and during conference calls.
- Obtain passwords for the CITR web site and frequently review CITR activity.
- Provide data entry.

2.2. Coordinating Center

The CITR Coordinating Center (CITR-CC), located at The EMMES Corporation, Rockville, Maryland, is responsible for developing the Manual of Procedures and AdvantageEDCSM User's Guide, collecting and analyzing registry data, ensuring that the provisions of the Manual of Procedures are carried out by all participating transplant centers and coordinating Registry activities. Coordinating Center staff includes professionals in biostatistics, epidemiology, data management, computer programming/information technology, administration and communication coordination. Consultants may be sought for appropriate specialized tasks.

All transplant center personnel, Coordinating Center staff and Committee memberships are listed in the CITR Roster maintained by the CITR-CC and available for viewing and printing at the CITR web site, (www.citregistry.org).

2.2.1. Registry Implementation

Coordinating Center staff has the responsibility to develop and maintain the data processing and database management systems for the Registry, provide statistical leadership in study planning and analytical methodology, and collect, edit, analyze and store all data received from the transplant centers. Some of the specific functions of the Coordinating Center staff are to:

- Collaborate with other investigators in developing and updating Registry procedures, case report forms, the Manual of Procedures, and the AdvantageEDCSM User's Guide.
- Coordinate and conduct center initiation visits, as well as interim data audit visits.
- Coordinate communications among the transplant centers.
- Monitor for adverse events reported by the transplant centers and distribute electronically the pertinent information to participating transplant centers in a timely manner.
- Review all data transmitted via the Internet for completeness and accuracy.
- Distribute data discrepancy reports to the transplant centers.
- Create and maintain computerized data files of CITR data.

- Prepare and distribute Annual Reports and bi-annual updates and to the transplant centers.
- Prepare and distribute monthly accrual and adverse event reports to the transplant centers, SAC and NIDDK.
- Periodically analyze the frequency of specified events and report to the Scientific Advisory Committee.
- Prepare recruitment, technical and statistical reports for meetings.
- Assist in preparing scientific reports for publication and presentation.
- Distribute periodic data compliance reports.
- Maintain and update the Internet Data Entry System.

2.2.2. Coordination and Administration

One of the functions of the Coordinating Center is to meet the many logistical, administrative, and communications requirements of the CTR. To maintain efficient communication among the participating transplant centers, the Scientific Advisory Committee and other various CTR committees, the Coordinating Center maintains a roster of all CTR personnel. This roster lists the names and addresses of all participating transplant centers, the names and e-mail addresses of the CTR staff members, and the names and e-mail addresses of current Committee members by Committee designation.

It is also the Coordinating Center's responsibility to provide logistical support to the CTR leadership. In this effort, the Coordinating Center will:

- Determine optimal meeting dates.
- Communicate information about meetings to the relevant Committee Chair and meeting participants.
- Provide logistical support during the meeting.
- Prepare and distribute materials prior to each meeting.
- Prepare and distribute minutes of the meetings.
- Follow-up on all action items after each meeting.
- Coordinate conference calls.

The Coordinating Center supports the preparation, duplication and dissemination of administrative and technical reports and manuscripts. These documents include:

- Protocol
- Manual of Procedures
- Transplant center application materials
- AdvantageEDCSM User's Guide
- Meeting minutes
- Newsletter
- Statistical reports

- Bibliographies
- Abstracts
- Manuscripts for publication
- Slides for presentations
- Roster of CITR personnel

Coordinating Center staff works closely with clinicians, writing committees, protocol development committees, scientists and authors. The staff routinely helps to:

- Compile and organize materials.
- Coordinate reviews and incorporate comments.
- Summarize background materials.
- Write administrative reports.
- Edit technical language to accommodate lay readers.
- Ensure that presentations are effective visually.

3.0 PROJECT POLICIES

3.1. Transplant Center Registration

Each transplant center interested in joining the CITR must obtain and complete the Transplant Center Application materials. This packet may be obtained by completing a form on the CITR web site (www.citrregistry.org), or by calling the CITR Coordinating Center. Registration to become a CITR transplant center must be completed before islet transplant recipients can be registered in the CITR database. The required documentation should be submitted to:

CITR Coordinating Center
 (Attention: CITR Project Manager)
 401 North Washington Street, Suite 700
 Rockville, MD 20850
 Tel: (800) 459-CITR
 Fax: (877) 665-4596
 citr@emmes.com

Once the required registration materials have been received, the Coordinating Center verifies that the information is complete and registers the transplant center. Any questions concerning the Transplant Center Application Packet should immediately be forwarded to the Coordinating Center. Following receipt of registration materials by the Coordinating Center, a site initiation visit is scheduled. Upon the completion of the initiation visit and all registration materials, the transplant center is authorized to begin registering participants and entering data.

3.1.1. CITR Transplant Center Application Packet

The CITR Transplant Center Application Packet contains information to introduce potential transplant centers to CITR, and provides instructions for successful completion of the application forms.

The CITR Transplant Center Application contains the following items:

- CITR Mission and Goals
- CITR Fact Sheet (Benefits/Structure)
- CITR Leadership Roster
- Transplant Center Application Information Sheet
- Transplant Center Registration Flow Chart
- Transplant Center Registration Form
- Islet Transplant Summary Form (hard copy and floppy disk)
- Letter of Agreement (hard copy and floppy disk)
- Payment Information Form
- Sample Consent Form (hard copy and floppy disk)
- CITR Protocol Template (hard copy and floppy disk)
- IRB/ERB Submission Review

3.1.2. Institutional Review Board (IRB)/Ethics Review Board (ERB) Review

Each transplant center is required to obtain IRB/ERB review prior to data reporting in the Registry. Documentation of the IRB/ERB review must be available at the transplant center and should be sent to the Coordinating Center prior to initiation of CITR. This documentation may be in the form of an IRB/ERB approval letter or an IRB/ERB waiver letter. Sites submitting the Registry protocol to their IRBs/ERBs are required to maintain annual documentation of continuing IRB/ERB approval or waiver. This documentation must be available prior to study initiation and within one month of the annual anniversary of the original approval date. A photocopy of the IRB/ERB letter of approval or waiver to the Investigator is acceptable. Annual reviews will be maintained at the transplant center and a copy forwarded to the Coordinating Center. If an annual review copy is not submitted to the Coordinating Center by the expiration date, data entry rights will be suspended for the Center until a copy is received.

3.1.3. Approved Consent/Assent Form

For centers requiring IRB/ERB approval, a copy of the IRB/ERB approved consent/assent form approved by the IRB/ERB must be maintained at the transplant center. A copy of the consent/assent form is not required at the Coordinating Center, but should be available during all site visits to the transplant center by the Coordinating Center. It is important to keep all IRB/ERB correspondence attached or in the same place as the approved Registry protocol and consent/assent form, for record-keeping purposes.

3.1.4. Health Insurance Portability and Accountability Act (HIPAA)

FOR US ISLET TRANSPLANT CENTERS ONLY

It is the responsibility of each participating US transplant center to know and understand their institution's response and implementation of the Health Insurance Portability and Accountability Act (HIPAA). All US CITR participating transplant centers must be HIPAA compliant to report data to CTR. There are many resources on the Web to guide you and your transplant center to obtain this compliance in addition to the guidance given by your institution and IRB. Some sites include: <http://aspe.hhs.gov/admnsimp/>, <http://www.nchica.org>, <http://www.amc-hipaa.org/> and <http://irb.mc.duke.edu>.

3.1.5. CTR Payment System

Letters of Agreement signed by the Coordinating Center and individual CTR clinical sites will specify the payment schedules for contribution of data to the Registry. Stipends for travel to the CTR Annual meeting are provided by the contract through the Coordinating Center. There is no further responsibility for any costs, services or activities of the Participating Center.

3.2. Adherence to Manual of Procedures

The CTR Executive Committee approves every Version of this Manual of Procedures. It is essential to the success of the Registry that the procedures outlined herein are adhered to by all transplant centers. If any CTR investigator finds, for whatever reason, that adherence to these procedures is difficult or not possible; they should discuss the problem with the SAC Chair or the Principal Investigator of the Coordinating Center.

3.3. Data Integrity

The Principal Investigator of each transplant center is responsible for the integrity of the information recorded on the CTR data forms and submitted to the Registry. Random audits of the data collected on the forms will be performed. Any personnel at a transplant center who is concerned about potential data anomalies at the transplant center that may jeopardize the integrity of the CTR database must immediately bring these concerns to the attention of the SAC Chair or the Executive Committee.

3.4. Protection of Human Subjects

In any publications resulting from the Registry, data will be grouped. No Registry patient or donor will ever be identified personally as the CTR-CC maintains no personal identifiers. In addition, the collective CTR data will be managed in perpetuity using the highest standards of protection of research subjects as required of the EMMES Corporation (www.emmes.com) as a contractor to the United States National Institutes of Health.

3.5. CITR Data Ownership

Registry data constitute a copy of the original medical information and as such belong to the NIDDK and may be used collectively for reporting of aggregate results. No individual participant data or any single transplant center's data (other than performance measures) are available to anyone other than Coordinating Center staff in conducting the work of the Registry. Individual transplant centers retain the right to use and publish their own data. All decisions regarding the use of the Registry data rest with the Publications/Presentations Committee with approval by the Scientific Advisory Committee. The P&P Committee approves and reviews all study proposals, publications or presentations based on analyses of the Registry data.

3.6. Scientific Publications and Presentations

3.6.1. Organization

The Collaborative Islet Transplant Registry's Executive Committee will approve and maintain a Publications & Presentations Committee. This committee has responsibility for:

- Developing procedures for generating scientific publications and presentations emanating from the design and data collection of CITR, and
- Editorial review of abstracts and manuscripts submitted for presentation and publication.

3.6.2. Committee Tasks

The Publications & Presentations Committee represents the CITR participating centers corporately, and is empowered to set the agenda and priorities of analysis and distribution of results on behalf of the Registry, in accordance with their charge granted by the NIDDK through their contract for CITR activities.

The specific tasks of the Publications/Presentations Committee are to:

- Maintain a Statistical Analysis Plan for conducting all analysis and writing reports (including the CITR Annual Report).
- Establish priorities and timelines for data analysis.
- Identify issues, hypotheses and concepts to be addressed in CITR reports.
- Invite suggestions for additional analyses from CITR investigators.
- Identify, propose, and appoint members and chairs of writing teams for developing specific CITR Reports, as necessary.
- Review manuscripts and abstracts submitted for publication and presentation for scientific content and conformance to CITR editorial and publication policies.

The Publications/Presentations Committee, in conjunction with the Executive Committee, will also perform the following analysis planning functions:

- Prepare outlines of plans for papers and specific plans for tabulations and computations. The plans for tabulations and computations should specify the

variables to be analyzed and include definitions, dummy tables, and algorithms, as appropriate.

- The Executive Committee will review and approve these plans before implementing them. In case of competing demands on the CITR Coordinating Center for tabulations and computations from different writing teams, the Scientific Advisory Committee Chair will assign a priority score for all competing work.
- Review activities and progress of writing teams.

3.6.3. Publications

Procedures for the development of study publications will be reviewed, amended and approved by the Publications & Presentations Committee. Any member of the CITR Group may submit a proposal to the Chair of the Publications & Presentations Committee, through the CITR Coordinating Center, for an abstract, manuscript for publication, or a presentation. To be considered for approval the application must:

- State the objective(s) of the research/analyses.
- Identify the specific items in the CITR database, by form name and question number that would be applicable to address each objective.
- Provide the name, date and location of the meeting, or the intended journal or book for publication.
- Provide the date of the deadline for abstract or publication submission.

To aid the investigator, he/she should complete the Request for Analysis Form online at the CITR website (www.citregistry.org) or complete and submit the form to the CITR Coordinating Center Principal Investigator. Applications must be submitted to the Publications/Presentations Committee via the Coordinating Center at least 30 days prior to the deadline for submission.

The Publications/Presentations Committee members will review proposals and approve, approve with suggestions, or disapprove with the reasons for disapproval stated. The Committee's review will be completed within 10 business days of application receipt. If approved, the Chair will notify the CITR Coordinating Center Director and work may begin. If the application is disapproved, the applicant may appeal to the Scientific Advisory Committee. The CITR Coordinating Center may at any time during the proposal or analysis phase recommend to the Publications/Presentations Committee and the Scientific Advisory Committee withdrawal of the application due to concerns regarding data quality or inference.

Publications (excluding abstracts) should include the following footnote to the acknowledgement of CITR* in the title: The Collaborative Islet Transplant Registry (CITR) is a voluntary effort of the participating islet transplant centers in North America, Europe and Australia. It is supported by the National Institute of Diabetes, Digestive and Kidney Diseases, with supplemental funding from the Juvenile Diabetes Research Foundation.

Each year the Publications/Presentations Committee will recommend a journal to submit the salient results of the CITR Annual Report. They will also recommend key meetings in which to present and promote the CITR Annual Report and data.

3.6.4. Reports and Authorship

CITR reports will either be primary or secondary reports. Primary reports deal with the Registry objectives and goals and consist of any analyses of data collected in a standard fashion for the Registry. Secondary reports will consist of investigator-initiated analyses of data collected by the Registry not reported through any of the primary reports. Before publication, copies of all primary reports are sent to the Publications/Presentations Committee. Reprints of published papers are mailed to each participating transplant center for distribution to staff and outside consultants. Five reprints of each paper are sent to the CITR Coordinating Center for the CITR library.

Primary and secondary CITR reports will be numbered serially. All reports will acknowledge the participation of those transplant centers that participated in the Registry present and past (as long as they contributed data to the Registry). Members of writing teams will also be acknowledged. Primary reports will be authored by "The CITR Research Group." Secondary reports will be authored by the principal investigator(s) initiating the analyses, coordinating center statistician(s) performing the analyses, and "The CITR Research Group."

Any participating transplant center may question authorship of a CITR publication. Such controversies first will be submitted in writing to the Publications/Presentations Committee. If all parties are not satisfied by the determination of the Publications/Presentations Committee, the matter may be appealed to the Scientific Advisory Committee. The SAC will give its recommendation to the Executive Committee, whose decision will be final and binding on all involved.

4.0 QUALITY ENHANCEMENT

4.1. Overview

The goal of the CITR quality enhancement program is to maintain the scientific integrity of the Registry. The principles of the CITR quality enhancement program are:

- Providing uniform definitions.
- Providing uniform criteria.
- Maintaining uniform procedures.
- Maintaining complete follow-up of all registered islet transplant recipients.

During the course of the Registry, many anomalies can occur that may impair the validity of the data collected and thereby the scientific integrity. Among these are:

- Missing certain observations on the data screens/CRFs.
- Failure of participants to appear for follow-up visits.
- Excessive waiting or other inconveniences on part of the participants.
- Participants losing confidence in the transplant center or its staff.

The quality enhancement program for CITR is similar to programs adopted in other multi-center studies and is intended to prevent or minimize anomalies that may weaken

the quality of the data collected either because of missing or invalid observations. The program is based on the following five principles:

- Responsibility and accountability of the personnel at the transplant centers and the Coordinating Center for implementing the Registry and maintaining the integrity of the data collected.
- Open lines of communication between the Coordinating Center and the transplant centers.
- Routine pilot testing of forms and procedures.
- Frequent, timely and up-to-date review of the quality of the data.
- Random medical chart review of participant laboratory and follow-up data to assure accuracy and compliance with the Registry protocol.
- An interactive process between the Compliance Committee and the transplant Coordinators'/Data Managers' Group focusing on real improvements in data quality as the Registry progresses.

4.2. Preventing Dropouts and Missed Visits

A primary objective of CITR is to study the clinical course of patients undergoing islet cell transplantation. To achieve this objective, it is essential that dropout rates are low, and that follow-up data are complete. Missing information can bias the analysis of Registry data. When data are incomplete, it is difficult to predict the direction of any bias resulting from the incompleteness. The only correct way to deal with missing information is not to have any. It is understandable that with a registry, some data may not have been collected or can not be retrieved. However, there may be ways to minimize the number of these cases. First, preventing dropouts is a responsibility shared by the entire transplant center staff, and this topic should be discussed frequently at staff meetings. When participants move to a location near another CITR transplant center, efforts should be made to transfer them to that center.

Transplant center personnel can help prevent missing data by doing the following:

- Rescheduling appointments, when necessary, in ample time so that the participant can revise his or her own schedule.
- Promptly following up on all missed data items.
- Telephoning, writing or faxing primary care physicians to obtain missing participant data.

The Compliance Committee will implement additional techniques and mechanisms as they may find necessary or helpful for clinical sites to improve the capture and reporting of scheduled data.

4.3. Internal Transplant Center Monitoring

Each Principal Investigator is responsible for ensuring that all Registry procedures are adhered to at the transplant center. Other transplant center staff members are responsible for reporting problems that could affect the quality of the data to the Principal Investigator.

4.4. External Transplant Center Monitoring

Data auditing at the Coordinating Center, conducted under the direction of the Project Manager, involves checking the data transmitted from the transplant centers to the Coordinating Center for completeness, adherence to the Manual of Procedures and internal consistency. This is performed via computer. The computer edit program generates "error messages" regarding incomplete, questionable, or inconsistent data.

Part of the auditing process is to analyze the frequency of errors according to their type to determine if certain types of errors keep recurring. If they do, this information is communicated to the transplant centers concerned and suggestions for improvement are made. Also, the Coordinating Center will monitor for timeliness of data submissions.

It is expected that data will be submitted by the transplant centers as it is collected when islet transplants are performed and follow-up visits (according to CITR protocol) are conducted. Getting this data entered in the system should not take more than 60 days from the date of the visit or the date of the infusion.

4.5. Registry Compliance

Each transplant center that participates in CITR should optimize its institution's resources for successful compliance. Participating institutions are encouraged to incorporate CITR into current patient/data flow systems, and ensure prospective data collection.

5.0 DATA ANALYSIS AND REPORTING

The CITR analysis plan is designed to carefully monitor Registry accrual, data quality and timeliness, adverse events and other outcomes. While detailed analyses will be performed periodically, study progress will be monitored continuously. Technical and administrative reporting requirements for CITR consist of both interim and Annual Reports of the Registry efforts.

5.1. Statistical Analysis Plan

The CITR Statistical Analysis Plan includes data quality, study progress, adverse events and participant outcome analyses. A comprehensive Annual Report summarizing data received by the Coordinating Center will be issued annually to all participating transplant centers. In addition, biannual reports summarizing key aspects of the Registry's experience compared to individual center experience will be issued separately to each individual center. Database assessments will be performed by the Coordinating Center to evaluate database quality on a monthly basis. In addition to these planned analyses, the Coordinating Center will expect to conduct various unplanned analyses precipitated by evolving Registry needs. Requests for such analyses will likely come from the Publications/Presentations Committee or the Scientific Advisory Committee. However, at any time, the transplant center has access to all of its own submitted data.

5.1.1. Specification of Analysis Database

Prior to performing a scheduled analysis, the master database file is copied into an analysis file. This analysis file is date-stamped with a closure date to indicate the last day for which data were included. The master file continues to incorporate new data from the centers while the analysis file is frozen.

The closure date provides a reference with regard to the currency of the data on which the analyses are based. Typically, the choice of a date to close the file for analysis is dependent on the type and quantity of the analyses to be performed. Files will likely be closed two months prior to a scheduled meeting.

5.1.2. Reports for Publication

The Coordinating Center will work with the Publications/Presentations Committee and the Scientific Advisory Committee in preparing a proposed schedule of analyses for disseminating CITR information to the scientific community. This schedule will be based on the Registry and data maturity.

5.2. Expected Assessments of the Database for Quality Control

Assessments of the database will occur on scheduled intervals. These assessments will be targeted at maintaining database integrity, monitoring of transplant center adherence to the protocol and assessing cumulative baseline (e.g., participant characteristics), outcome variable assessments (e.g., rejection incidence), morbidity and mortality.

5.2.1. Database Quality

As previously noted, database quality will be maintained through a variety of analyses that target anomalies (missing or inconsistent values), delinquent data and key entry errors. Reports summarizing anomalies found are transmitted to the transplant centers for resolution. A part of this process will be to analyze the frequency of errors according to type to determine if certain types of errors are recurrent. Modifications to the data entry system will be made if the errors occur frequently across transplant centers. If errors are localized within a transplant center, steps will be taken to resolve the problems by additional training to the center or modifications to the data system.

5.2.1.1. Duplicate and error checks

Although the CITR data system is designed to prohibit duplicate forms, a check will be made at the Coordinating Center to insure that no undetected duplicates remain. Following this check, another check of the database will examine the individual fields and computed values within each record for illegal or conflicting entries. Variables found to be either in error or inconsistent with other data will be compared to an Anomaly Exception File.

The Anomaly Exception File is a means of documenting acceptable anomalies on a participant and date basis. The Coordinating Center's Data Manager will maintain the Anomaly Exception File as a record of resolved queries and contains the participant identification number, and form and field identifiers. Also

included is the reason for the exception and the date the reason was entered. A second date field is available if the exception has an expiration date.

5.2.1.2. Delinquent data

The determination of delinquent data will be performed at the form level and the field level. Delinquent forms will be identified and compared to an exception list. All missing forms will be grouped by site. A missing form report will be available for each transplant center to view and print. A missing form will continue to be requested either until the data for the form are transmitted and integrated into the Coordinating Center's central master database or until an exception is granted and entered into the Missing Form Exception File.

The second level of delinquent data will be at the field or variable level. Fields will be checked for values that indicate that they are missing and were not keyed into the form. As with the missing form and error/anomaly review, this program will identify the missing values by a participant identification number, form and variable. Reports that identify missing values are generated by site and will be available to the transplant center to view and print. Missing data may be added to the database at any time. Missing values will continue to be reported until completed or until an exception is granted.

5.2.2. Operational Statistics

Analyses directed at monitoring the smooth and efficient operation of the Registry, e.g., the enrollment, the completeness of data forms, the quality of the completed data forms, delays in completing data forms, numbers of missed visits, study dropouts, etc., will be performed routinely. These reports will assist in identifying local problems that require resolution and will allow routine monitoring of the Registry to identify problems. Some of the reports that are generated include:

- Number of islet transplant participants enrolled by transplant center and cumulative totals.
- Percentage of error-free data forms (e.g. forms without missing data or data anomalies) by individual transplant center and by all transplant centers.
- Numbers of missed visits by transplant center and visit, and by all transplant centers.
- Number of dropouts, by individual transplant center and by all transplant centers.

5.2.3. Participant Characteristics

The demographic characteristics of participants will be analyzed.

- Age, sex, race, etc.
- Medical history.
- Laboratory information.

5.2.4. Outcome Variables, Morbidity and Mortality

Outcome variables, morbidity and mortality assessments will be performed as determined by the Scientific Advisory Committee, investigator suggestions, and Executive Committee discussions. In all presentations of CITR data, the number of participants on which the analysis is based, whether the result is a mean, a percentage, an incidence rate, or prevalence rate, etc., will be shown. Standard errors, confidence limits, or other measures of sampling variables will also be shown.

5.3. Reporting

5.3.1. Annual Reports

Annual Reports will include comprehensive summaries of data collected by CITR. Specifically the following topics will be addressed:

- Participant characteristics
- Donor factors
- Recipient factors
- Transplant factors
- Islet processing
- Immunosuppressant therapy
- Rejection
- Graft function
- Adverse events
- Morbidity, mortality and malignancy
- Loss to follow-up
- Multiple islet infusions
- Non islet transplants

5.3.2. Biannual Center Reports

Biannual Center Reports will be issued by the Coordinating Center to each participating transplant center. These reports will provide individual centers with a summary of their center's data as compared to Registry findings. Topics will include registrations, rejections, participant and graft survival, and hospitalizations.

5.3.3. Scientific Reports

After approval by the Publications/Presentations Committee, the Coordinating Center's Statisticians will assist the investigators in preparing scientific publications.

In collaborating with Principal Investigators on publications, the Statisticians provide not only the tabular and graphic presentations of data, but also the Registry methods and results sections. Completed documents will be submitted to the Publications/Presentations Committee for review and approval prior to publication submission.