



COLLABORATIVE ISLET TRANSPLANT REGISTRY

MANUAL OF PROCEDURES

Version 2.0

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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 and in five JDRFI (Juvenile Diabetes Research Foundation International) funded European islet transplant programs.

Initiated and funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), CITR was founded in September 2001. The islet/beta cell registry is coordinated by The EMMES Corporation of Rockville, Maryland with Dr. Bernhard Hering of the University of Minnesota as the Medical Director. The CITR Executive Committee is composed of Dr. Michael Appel (NIDDK), Dr. Donald Stablein (EMMES), Nicole Close (EMMES), Dr. Bernhard Hering (University of Minnesota), Dr. David Sutherland (University of Minnesota), and Dr. Angelika Gruessner (University of Minnesota). A committee of seven members, chosen by EMMES, in consultation with NIDDK, provides scientific direction to the Registry (this group will be referred to as the Scientific Advisory Committee or SAC) with Dr. Hering presiding as the Chair. Members include Dr. Reinhard G. Bretzel (University of Giessen, Germany), Dr. Michael Cecka (University of California, Los Angeles), Dr. Mary D. Ellison (United Network for Organ Sharing), Dr. Jerry Palmer (VA Puget Sound Health Care Systems), Dr. Camillo Ricordi (University of Miami), Dr. James Shapiro (University of Alberta), and Dr. Olle Korsgren (Uppsala University Hospital, Sweden and The Nordic Network).

In July 2004, JDRFI provided additional funding to CITR to include five JDRFI funded European islet transplant programs in the Registry.

Islet/beta cell transplantation is a complex procedure with many factors contributing to outcome. Compiling and analyzing data from islet transplant centers will accelerate the identification of both critical risk factors and key determinants of success, and thereby guide transplant centers in developing and refining islet/beta cell transplant protocols.

Islet/beta cell transplantation has become a rapidly developing field, making it difficult for non-experts to stay abreast of the most recent information. Data communicated by CITR will assist people with diabetes, health care professionals, payers and providers, professional societies, funding agencies, and governmental institutions in making decisions regarding islet/beta cell transplantation.

The inclusion of the term “collaborative” in the name of the Registry emphasizes the importance of collaboration in fulfilling the mission of CITR. Close collaboration with the transplant centers will ensure that relevant questions are addressed, that data submitted are accurate and complete, and that the needs of the transplant community are served. Collaboration with other initiatives, programs, and networks of the National Institutes of Health, (e.g., the Human Pancreatic Islet Cell Resource

Consortium (ICR), the Immune Tolerance Network (ITN)), the Clinical Islet Transplantation Consortium (CIT), and the Juvenile Diabetes Research Foundation International, will be instrumental in utilizing established infrastructures and in facilitating ancillary studies. Collaboration with the diabetes care community, the health insurance industry, the Centers for Medicare and Medicaid Services (formerly known as Health Care Finance Administration - HCFA), Health Resources and Services Administration (HRSA), and the US Food and Drug Administration (FDA) will ensure that the outcome measures used by CTR are appropriate, standardized, and relevant. Collaboration with United Network for Organ Sharing (UNOS) and the Canadian Organ Replacement Register (CORR) will avoid duplication of efforts with respect to the collection of donor and recipient information. Finally, collaboration with the International Islet Transplant Registry (ITR) in Giessen, Germany will ensure that the worldwide status of islet/beta cell transplantation is regularly updated.

To meet these objectives CTR encourages all transplant centers in North America that perform islet cell transplants to become a participating center. Participating transplant centers are provided with biannual summaries of data submitted to the central Coordinating Center and detailed Annual Reports containing a comprehensive analysis of data submitted by all participating centers.

1.2. Specific Goals

All islet transplants performed since January 1, 1999 should be captured by the Registry. Specific goals of the Registry are as follows:

- To develop and implement standards for reporting islet/beta cell transplants and their outcome.
- To collect and compile data on all islet/beta cell transplants in human recipients performed in North America and in five JDRFI funded European islet transplant programs.
- To increase the safety of islet/beta cell transplantation by electronically distributing the pertinent information of submitted adverse event reports to all participating clinical sites in a timely fashion.
- To perform scientific analysis on islet/beta cell transplant data, with particular emphasis on:
 - Safety of islet/beta cell transplant product and procedures, and protocol-regulated treatment products.
 - Number of islet/beta cell transplants and retransplants performed, categorized by transplant institution, donor tissue source and handling, recipient category, transplant technique and site, and recipient treatment protocols.
 - Efficacy of islet/beta cell transplants as defined by standardized outcome measures and as determined by donor factors, recipient demographics, donor-recipient matching, islet/beta cell processing and product

characteristics, transplant technique and site, recipient treatment, and post-transplant events.

- To communicate comprehensive and current information on islet/beta cell transplantation to transplant centers, the diabetes and general health care community, and the interested general public via the CITR web site (<http://www.citregistry.org>), publications, and presentations.
- To stimulate prospective and retrospective studies on emerging issues of importance.

1.3. Organization of CITR

CITR is comprised of transplant centers that have responsibility for registering islet transplant recipients and collecting follow-up information on their outcomes. In addition to the transplant centers, a Coordinating Center (located at The EMMES Corporation) provides support for logistics, data capture, quality-control monitoring, statistical design and analysis, and other activities, as described later in this manual.

The Scientific Advisory Committee (SAC) provides scientific oversight for the conduct of the Registry and the Executive Committee provides oversight for the day-to-day activities of the Registry.

1.4. Registry By-laws

1.4.1. 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.

1.4.2. 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 JDRFI. The EMMES Corporation is the core component of the Registry and will be known as the Coordinating Center, providing statistical support, data management and organizational resources.

1.4.3. Meetings

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

1.4.4. 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 (one CITR Principal Investigator and one CITR Transplant Coordinator/Data Manager). Participating Members are persons in participating transplant centers. Each participating center must identify at least one Principal Investigator and one Transplant Coordinator/Data Manager as contact persons for the Registry. Participating Members may serve on committees of the Registry.

1.4.5. Officers

There shall be a Scientific Advisory Committee (SAC) appointed by EMMES, 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 Director shall serve as ex officio 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 annual meeting, be responsible for overseeing the final agenda and serve as the official representative of the Organization.

There shall be an Executive Committee, comprised of the Project Officer from NIDDK, Dr. Michael Appel; the SAC Chair and Medical Director of the Coordinating Center, Dr. Bernhard Hering; Drs. David Sutherland and Angelika Gruessner from the University of Minnesota; Dr. Donald Stablein and Ms. Nicole Close from the EMMES Corporation. This Committee will oversee the daily functions of the CITR, answer Registry specific questions, and coordinate aspects of the Registry with the SAC.

1.4.6. Committees

There shall be four standing Committees.

Compliance Committee: The seven members of the Compliance Committee shall be elected by ballot by the participating transplant centers. Each center will have one vote. No more than one representative from any one center can serve on the Compliance Committee during a term. Election shall require a plurality of votes cast by the voting due date. Members will serve a minimum of one year on the Committee and may remain on the Committee for a maximum of two years. By staggering lengths for Committee membership, the Registry hopes to maintain knowledge on the Committee without complete turnover at the next election.

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. 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.

Publications/Presentations Committee: This seven-person committee is nominated from the participating transplant centers. Their charge is to develop and implement a clear and concise set of guidelines for the publication and presentation of data from the Registry. The Chair will be elected by the Committee to hold a two-year term of office. Election shall require a plurality of votes cast by the voting due date. 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 Monitoring Committee: This eight-person Committee consists of Principal Investigators, Islet Processing Investigators and at least one Transplant Coordinator/Data Manager nominated from the participating transplant centers. The Chair will be elected by the Committee to hold a two-year term of office. The Committee is responsible for monitoring changes in the standard practice of islet transplantation, which includes islet isolation, purification, transplant technique, immuno suppression 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 committees as are necessary to carry out the purposes of CITR as stated above.

1.4.7. 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.

1.5. 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.

1.6. 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. 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. Detailed instructions for data entry are found in the CITR AdvantageEDCSM User's Guide. Appendix A contains an overview of the required forms for registration and follow-up and a forms schedule.

1.7. Follow-up Procedures

Each registered participant is followed at six months post first islet infusion and twelve months post first islet infusion. In addition, full data collection is conducted at six months post last infusion, 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

The participating investigators and transplant centers in CITR collaborate through a non partisan organization designed to maintain a continuity of operations and to facilitate effective communication and cooperation among the participants. CITR is financially supported by the National Institute of Diabetes and Digestive and Kidney Diseases and has supplemental funding from JDRFI. The EMMES Corporation provides statistical and data management support. The Executive Committee is responsible for the day to day functions of CITR, while the Scientific Advisory Committee is responsible for the scientific integrity of CITR.

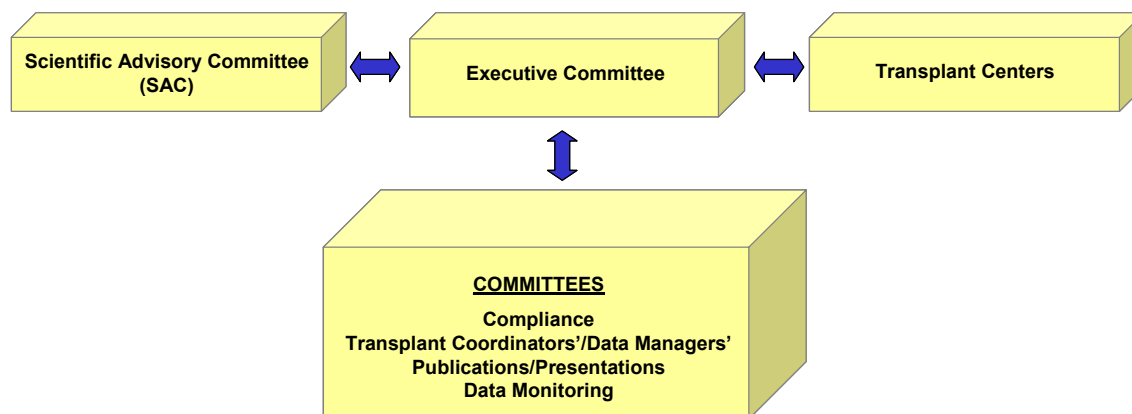


Figure 1: CITR Structure

2.1. Transplant Center

The success of a multi-center endeavor depends on the 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). There may be additional staff designated as co-investigators, data managers or administrative personnel.

2.1.1. Functions of the Principal Investigator

The responsibilities of the designated PI are to:

- Supervise the participant registration process.
- 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 protected web site and frequently review the CITR Interactive site.

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 current transplant center roster of personnel, address, telephone number(s) and notify the Coordinating Center with any changes.
- Maintain a file of correspondence with the Coordinating Center.
- Obtain necessary information about deceased participants (e.g., 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 protected web site and frequently review the CITR Interactive site.
- Provide data entry.

2.2. Coordinating Center

The Coordinating Center, 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 used to supplement the staff for appropriate specialized tasks. A listing of Coordinating Center staff is provided in the CITR Roster (see Appendix B). The CITR roster is available to view and print on the CITR web site, at www.citregistry.org.

2.2.1. Registry Implementation

Coordinating Center staff have 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 for CITR data.
- Prepare and distribute bi-annual and Annual Reports 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 CITR. To maintain efficient communication among the participating transplant centers, the Scientific Advisory Committee and other various CITR committees, the Coordinating Center maintains a roster of all CITR personnel. This roster lists the names and addresses of all participating transplant centers, the names and e-mail addresses of the CITR staff members, and the names and e-mail addresses of current Committee members by Committee designation. This roster may be viewed and printed from the CITR web site.

It is also the Coordinating Center's responsibility to provide logistical support to the CITR 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:

- 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.citregistry.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 Director)
401 North Washington Street, Suite 700
Rockville, MD 20850
Tel: (800) 459-CITR
Fax: (301) 251-1355

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 requires IRB/ERB review prior to participation 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 transplant center to know and understand their institution's response and implementation of the Health Insurance Portability and Accountability Act (HIPAA). All CITR participating transplant centers must be HIPAA compliant to join CITR. 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/admsimp/>, <http://www.nchica.org>, <http://www.amc-hipaa.org/> and <http://irb.mc.duke.edu>.

3.1.5. CITR Payment System

An initial payment of \$2000 (USD) will be made to each center upon receipt of the Transplant Center Registration Form, Payment Information Form, signed Letter of Agreement, and IRB/ERB documentation. Thereafter, the center shall receive a payment of up to \$250 (USD) for each participant registered for CITR. The payments shall be disbursed as follows: the center will receive an initial payment

of \$150 per participant upon receipt of the Demographic and Registration Forms (DEM, ENR), Donor Form (CAD, LAL or LAU), Pre Infusion Form (PRE), Pre Infusion Lab Info Form (PRL), Infusion Form (TRN), and Induction Therapy Form (IND). Two additional payments of \$50 each will be made following receipt of Year 1 and Year 2 Follow-up data. There is no further responsibility for any costs, services or activities of the Participating Center.

3.2. Adherence to Manual of Procedures

The CITR Executive Committee has approved 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 CITR 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 CITR data forms. Random audits of the data collected on the forms may 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 CITR 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. Every effort will be made to maintain the confidentiality of CITR participant records. On occasion however, representatives from the Coordinating Center may wish to review the records.

3.5. CITR Data Ownership

Registry data are not the property of the Coordinating Center or the Scientific Advisory Committee. Study data submitted become the property of CITR and belong collectively to all participating transplant centers. All decisions regarding the use of the Registry data rest with the Publications/Presentations Committee. This committee must approve and review 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

All transplant centers and collaborators will be informed that Registry data are not the property of the CITR Coordinating Center or the Scientific Advisory Committee. Registry data submitted become the property of the CITR Group and belong collectively to all participating transplant centers. The Publications/Presentations Committee represents all of the participating centers, and is empowered to exercise the collective rights of ownership of the study data on behalf of the participating centers.

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

- Identify issues, hypotheses and concepts to be addressed in CITR reports.
- Prepare a plan for writing a series of CITR Reports (including the CITR Annual Report).
- Invite suggestions for additional analyses from CITR investigators.
- Identify, propose, and appoint members and chairmen 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 Director, 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 or complete and submit the form to the CITR Coordinating Center Director (see Appendix C). Applications must be submitted to the Publications/Presentations Committee via the Coordinating Center at least 60 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 comprising over (XX) islet transplant centers in North America and Europe. It is supported by NIH contract number N01-DK-1-2472.

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

Abstracts of papers to be presented at scientific meetings and manuscripts submitted for publication that pertain to CITR or are based on CITR data, (whether they pertain to a single participating transplant center, several transplant centers, or all transplant centers) must be reviewed by the Publications/Presentations Committee before presentation and/or before publication. The only exceptions are oral or written presentations to local groups reporting on local data results, provided the presentation does not associate CITR with the reported results. Such presentations do not need to be reviewed by the Publications/Presentations Committee.

Approval is needed to assure that publications and presentations will not:

- Complicate the interpretation of CITR data.
- Violate participant's rights.

- Jeopardize the public reputation of CITR.
- Substantially divert Registry resources at the transplant center or at the CITR Coordinating Center.

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." In the future, 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 raise controversies over 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, or nearly all, participants.

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.
- Failure of participants to appear for follow-up visits.
- Excessive waiting or other irritations suffered by 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.
- Analysis of the quality of the data.
- Medical chart review of participant laboratory and follow-up data to assure accuracy and compliance with the Registry protocol.

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.

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 Lead Data Manager or Director, 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. Analysis Plan

The CITR 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, 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 duplicates, 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
- Immunosuppression 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.

APPENDIX A

FORMS LISTING AND SCHEDULE



FORMS LISTING AND SCHEDULE OF FORM SUBMISSION

FORM NAME	TIME OF INFUSION	POST-INFUSION
Demographics/Registration (DEM)/(ENR)	X	
Deceased Donor (CAD)	X ^{*,a}	
Living Allo-Donor (LAL)	X ^{*,a}	
Living Auto-Donor (LAU)	X ^{*,a}	
Islet Processing/Testing (IPT)	X	
Pre Infusion (PRE)	X	
Pre Infusion Lab Info (PRL)	X	
Infusion (TRN)		X
Induction Therapy (IND)		X
Follow-up Post First Infusion (FOI)		X
Follow-up Post Last Infusion (FOL)		X
Follow-up Post Last Infusion Lab Info (FUL)		X
Insulin Administration (INS)		X*
Islet Graft Dysfunction (IGD)		X*
Non Islet Transplant (NIT)	X*	X*
Non Islet Transplant Follow-up (NIF)		X*
Adverse Event Form (AEF)	X*	X*
Lost to Follow-up (LTF)		X*
Death (DTH)	X*	X*
Transfer (TNF)		X*

* If applicable, complete form.

^a Completion of one of these forms is required.



POST-INFUSION FORM SUBMISSION SCHEDULE

FORM NAME	SCHEDULE
Infusion (TRN)	Data captured at the time of each islet infusion through 30 days post-infusion. Data submitted to Coordinating Center no later than 60 days post islet infusion.
Induction Therapy (IND)	Data captured at the time of each islet infusion through 30 days post-transplant. Data submitted to Coordinating Center no later than 60 days post islet infusion.
Follow up Post First Infusion (FOI)	Data captured at 6 months and 12 months after the initial infusion. Do not complete this form if an FOL form is completed on the same date.
Follow-up Post Last Infusion (FOL)	Data captured at 6 months, 12 months, and yearly thereafter for post last islet infusion. This schedule resets based on the date of the last islet infusion the participant receives.
Follow-up Post Last Infusion Lab Info (FUL)	Data captured at 6 months, 12 months, and yearly thereafter for post last islet infusion. This schedule resets based on the date of the last islet infusion the participant receives.
Insulin Administration (INS)	Completed at the same time as the Follow-up Post First Infusion form (FOI) or Post Last Infusion form (FOL) when a participant is currently taking insulin or has taken insulin during the assessment period according to CITR definitions.
Non Islet Transplant (NIT)	Completed when participant has a non islet transplant.
Non Islet Transplant Follow-up (NIF)	Completed at least yearly for functional status of the transplant. Yearly updates should coincide with yearly CITR assessments.

Post Infusion Form Submission Schedule *(continued)*

FORM NAME	SCHEDULE
Adverse Event Form (AEF)	Submitted as needed, as soon as AE is reported to Transplant Coordinator and/or Regulatory authorities. Initial data may be reported with updates to the form as needed.
Islet Graft Dysfunction (IGD)	Submitted as needed, if participant has a suspected islet graft dysfunction per CITR definitions.
Lost to Follow-up (LTF)	Submitted as needed when every effort to locate and contact the participant has been exhausted. The Transplant Coordinator should notify and work with the Coordinating Center prior to submitting this form.
Death (DTH)	Submitted as needed, no later than 30 days post notification to the Transplant Coordinator.
Transfer (TNF)	Submitted after notifying the Coordinating Center.

APPENDIX B CITR ROSTER

SCIENTIFIC ADVISORY COMMITTEE (SAC) ROSTER

Bernhard J. Hering, MD
CITR Medical Director and SAC Chair
University of Minnesota
Box 195, Mayo 8195
420 Delaware Street SE
Minneapolis, MN 55455 USA
Phone: 612-626-5697
Fax: 612-626-5855
E-mail: bhering@tc.umn.edu

A.M. James Shapiro, MD, FRCS
Director, Clinical Islet Transplant
Program
University of Alberta
Department of Surgery
2000 College Plaza
8215 112th Street
Edmonton, AB T6G 2C8 CAN
Phone: 780-407-7330
Fax: 780-407-6933
E-Mail: amjs@islet.ca

Camillo Ricordi, MD
Scientific Director, Diabetes Research
Institute
Chief, Cellular Transplantation
University of Miami, School of Medicine
1450 NW 10 Avenue (R-134)
Miami, FL 33136 USA
Phone: 305-243-6913
Fax: 305-243-4404
E-mail: ricordi@miami.edu

Michael Cecka, PhD
Clinical Research Director
UCLA Immunogenetics Center
Mail Code 165222
1-520 Rehab Center
Los Angeles, CA 90095-1652 USA
Phone: 310-825-6585, 310-825-7651
Fax: 310-206-3216
E-mail: mcecka@ucla.edu

Reinhard G. Bretzel, MD, PhD
Direktor
Medizinische Klinik und Poliklinik III
Universitaet Giessen
Rodthohl 6
Giessen 35392 GER
Phone: +49 641 99-42750 or
+49 641 99-42840
Fax: +49 641 99-42759 or
+49 641 99-42849
E-mail:
reinhard.bretzel@innere.med.uni-giessen.de

Mary D. Ellison, PhD, MSHA
Assistant Executive Director for Federal
Affairs
United Network for Organ Sharing
UNOS Research Department
700 North 4th Street, 4th Floor
Richmond, VA 23219 USA
Phone: 804-782-4917
Fax: 804-782-4817
E-mail: ellisomd@unos.org

Jerry P. Palmer, MD
VA Puget Sound Health Care Systems
Endocrinology (III)
1660 South Columbian Way
Seattle, WA 98108-1597 USA
Phone: 206-764-2495
Fax: 206-764-2693
E-mail: jpp@u.washington.edu

Olle Korsgren, M.D., Ph.D.
Professor of Transplantation
Immunology Department of Clinical
Immunology
Uppsala University Hospital
SE-751 85 Uppsala, Sweden
Phone: +46 18 611 4187
Fax: +46 18 611 0222
E-mail: olle.korsgren@klinimm.uu.se

REGISTRY SPONSOR

Michael C. Appel, PhD
Director, Islet Biology and
Transplantation Research Program
Division of Diabetes Endocrinology and
Metabolism
National Institutes of Health, NIDDK
Two Democracy Plaza, Room 792
6707 Democracy Blvd., MSC 5460
Bethesda, MD 20892-5460 USA
Phone: 301-594-4740
Fax: 301-480-0475
E-mail: appelm@niddk.nih.gov

CITR COORDINATING CENTER

Nicole Close, MS
Principal Investigator, Director
The EMMES Corporation
401 N. Washington Street, Suite 700
Rockville, MD 20850 USA
Phone: 301-251-1161, ext. 225
Fax: 301-251-1355
E-mail: nclose@emmes.com

Don Stablein, PhD
Co-Principal Investigator
The EMMES Corporation
401 N. Washington Street, Suite 700
Rockville, MD 20850 USA
Phone: 301-251-1161, ext. 128
Fax: 301-251-1355
E-mail: dstablein@emmes.com

Stephen Wease, MPH
Lead Data Manager
The EMMES Corporation
401 N. Washington Street, Suite 700
Rockville, MD 20850 USA
Phone: 301-251-1161, ext. 226
Fax: 301-251-1355
E-mail: swease@emmes.com

James Cravens, MPH
Director
The EMMES Corporation
401 N. Washington Street, Suite 700
Rockville, MD 20850 USA
Phone: 301-251-1161, ext. 2968
Fax: 301-251-1355
E-mail: jcravens@emmes.com

Devin Hunt
Data Manager
The EMMES Corporation
401 N. Washington Street, Suite 700
Rockville, MD 20850 USA
Phone: 301-251-1161, ext. 157
Fax: 301-251-1355
E-mail: dhunt@emmes.com

Jessica Long
Data Manager
The EMMES Corporation
401 N. Washington Street, Suite 700
Rockville, MD 20850 USA
Phone: 301-251-1161, ext. 2956
Fax: 301-251-1355
Email: jlong@emmes.com

Omid Neyzari, MS
Application Developer
The EMMES Corporation
401 N. Washington Street, Suite 700
Rockville, MD 20850 USA
Phone: 301-251-1161, ext. 132
Fax: 301-251-1355
E-mail: oneyzari@emmes.com

Glenn Tucker
Programmer
The EMMES Corporation
401 N. Washington Street, Suite 700
Rockville, MD 20850 USA
Phone: 301-251-1161, ext. 237
Fax: 301-251-1355
E-mail: gtucker@emmes.com

Charles Wagner
Administrative Coordinator
The EMMES Corporation
401 N. Washington Street, Suite 700
Rockville, MD 20850 USA
Phone: 301-251-1161, ext. 2961
Fax: 301-251-1355
E-mail: cwagner@emmes.com

**COMPLIANCE COMMITTEE
Members (2005-2006)**

Michael Appel	NIDDK
E. Brian Flanagan	JDRFI
Fouad Kandeel	Southern California Islet Consortium
Eileen Markmann	University of Pennsylvania
David Radosevich	University of Minnesota
Marti Sears	Emory Transplant Center
Elyse Stuart	Northwestern University

**TRANSPLANT COORDINATORS'/DATA MANAGERS' COMMITTEE
(2005-2006)**

Eileen Markmann
The University of Pennsylvania

Terri Baker
Swedish Medical Center

David Baidal
The University of Miami

Susan Comninel
Columbia University

Barbara Culbreath
The University of Tennessee, Memphis

Arthur Dea
Center for Islet Transplantation at Harvard Medical
School

Parastoo Dinyari
The University of Alberta

Cheryl Durkop
Baylor College of Medicine/Methodist Hospital

Debbie Grice
Virginia Commonwealth University

Celia Hartigan
UMass Memorial Health Care

Elizabeth Holbrook
Emory Transplant Center

Debra Kemp
Washington University, St. Louis

Kathleen LaBranche
The University of Alberta

Lorraine Lesiecki
Southern California Islet Consortium

Marli McCulloch-Olson
Benaroya Research Institute

Maral Palanjian
The University of Pennsylvania

Jamen Parkey
The University of Minnesota

Melissa Roberts
The University of Chicago

Grace Sauzier
Carolinas Medical Center

Marti Sears
Emory Transplant Center

Jill Sheedy
Toronto General Hospital

KD Shiang
Southern California Islet Consortium

Winsor Simmons
University of Virginia

Robert Smith
Toronto General Hospital

Elyse Stuart
Northwestern University

Heather Turgeon
Center for Islet Transplantation at Harvard
Medical School

Terri Wakefield
National Institutes of Health

Laurie Weiner
University of Colorado Health Sciences Center

Elizabeth Wright
Toronto General Hospital

Tiffany Zgabay
Baylor College of Medicine/Methodist Hospital

Dylan Zylla
The University of Minnesota

PUBLICATIONS/PRESENTATIONS COMMITTEE
Members (2005-2006)

Rodolfo Alejandro (Chair)	University of Miami
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Nancy Bridges	NIAID
Elizabeth Holbrook	Emory Transplant Center
Ali Najj	The University of Pennsylvania
A. M. James Shapiro	The University of Alberta
Craig Smith	Southern California Islet Consortium

**DATA MONITORING COMMITTEE
Members (2005-2006)**

Marc Garfinkel (Chair)	University of Chicago
David Baidal	University of Miami
Enrico Cagliero	Center of Islet Transplantation at Harvard Medical School
Fouad Kandeel	Southern California Islet Consortium
Dixon Kaufman	Northwestern University
Jeff Longmate	Southern California Islet Consortium
Melissa Roberts	The University of Chicago
Marti Sears	Emory Transplant Center

APPENDIX C

REQUEST FOR ANALYSIS FORM



CITR REQUEST FOR ANALYSIS FORM

Complete this form and fax it to the CITR Director at 301-251-1355. We will review the form and then forward the form to the Publications/Presentations Chair for consideration.

NAME: _____ CENTER: _____

Date of Request: ____/____/____

Primary Author: _____

Collaborators, if any: _____

Target Publication/Presentation: _____

Target Publish or Presentation Date: ____/____/____

1. Research Question:

a. Primary Objective(s):

b. Secondary Objective(s):

2. Rationale (Explain why this analysis should be performed.)

3. Target Population (Specify the subset of patients to be included in this analysis. Are there any comparison groups? If yes, please specify.)

4. Outcome Variables (using the CITR CRFs, identify all variables that will be included in this analysis. Indicate which variable will be the primary outcome variable.)

CITR Form Name	Question Number/Variable