COLLABORATIVE ISLET TRANSPLANT REGISTRY

PROTOCOL/
MANUAL OF PROCEDURES

Version 5.0

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1.0 OVERVIEW

1.1 Benefits of the Collaborative Islet Transplant Registry

- Single, standardized, world-wide repository of comprehensive human islet transplant data since 1999
- Domains: clinical allo-islet, auto-islet, pancreatectomy (without auto), T1D on wait-list, xeno-islet
- Opportunity for member-site investigators to collaborate in writing and presenting results
- Single networking forum in human islet transplantation – all islet investigators welcome
- Center-specific original data, patient-wise summaries and center-wise summaries, updated regularly, available at www.ciretegistry.org
- Able to accommodate all clinical data on recipients (in addition to CITR-required time points and data elements)
- Able to accommodate both clinical and non-clinical islet data
- Conforms to good clinical practice standards

1.2 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.

Transplantation of islets of Langerhans is an evolving experimental medical procedure that provides hope for freedom from insulin injections and poor glycemic control, longer life expectancy and better quality of life, for persons with Type 1 diabetes. Despite the proof of concept of successful islet transplantation in 1999 [Shapiro et al, NEJM], long-term clinical success and retention of islet graft function remain elusive. Since those initial successes, a number of investigator groups in various countries have been advancing knowledge and effecting improvements with protocols testing variations in islet procurement, processing, implantation and immunosuppression. As with solid organ transplantation, progress is slow and dependant on gathering and sharing the collective knowledge and information derived from these experimental protocols.

The Collaborative Islet Transplant Registry (CITR) is a research effort funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), with supplemental funding from the Juvenile Diabetes Research Foundation International (JDRFI) to collect, analyze and disseminate complete and current information on human islet transplantation. Participation in CITR is voluntary, both by the islet

transplant centers and individual islet transplant recipients. Data management, statistical and logistic coordination is provided by the EMMES Corporation (Rockville, MD), who is responsible for the day-to-day activities of the Registry, as well as analysis and dissemination of results.

CITR began in 2002 and continues to recruit islet transplant centers to participate in the Registry. The goal is to collect and report data on all human islet transplants conducted since January 1, 1999. Initially, the two components of CITR were islet allograft and autograft recipients, including data on the respective donors and processed islets. In 2009, in response to requests by islet transplant centers and with the consent of the NIDDK, CITR expanded the database to accommodate data for a given islet recipient at any time point, and for recipients not giving consent for their data to be included in CITR. This expansion allows islet transplant sites to have a single, comprehensive source database for all their islet transplant research activities, obviating the need for duplicate databases. Additionally, the NIDDK has approved the use of the CUITD for data reporting on one or more natural history comparator groups; the ones identified to date are T1D on the transplant waiting list and pancreatectomy cases not receiving an autologous transplant.

An Annual Report is published and distributed to participating transplant centers, the scientific community, and the interested public. Past reports are available at www.CITRegistry.org. Scientific papers of salient results from the Annual Report and results from focus inquiries of the data are also submitted for publication in prominent peer-reviewed journals and presented at major meetings on islet transplantation.

This combined CITR Protocol/Manual of Operations 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, and details how the policies and procedures of the Registry are implemented.

1.3 Research Goals and Questions

The specific objectives of CITR are:

1. To develop and implement standards for reporting islet/beta cell transplants and their outcome.
2. To collect and compile data on all islet/beta cell transplants in human recipients performed in North America, the JDRF-funded European and Australian Centers, and any other centers that voluntarily participate in CITR. The period of interest is human islet transplantation since 1999.
3. To increase the safety of islet/beta cell transplantation by frequently distributing up-to-date summaries of submitted serious adverse event reports to all participating transplant centers in a timely fashion.

4. To perform scientific analyses on islet/beta cell transplant data, with particular emphasis on:
5. Safety of islet/beta cell transplant product and procedure and protocol-regulated treatment products.
6. Number of islet/beta cell transplants and retransplants performed, categorized by donor tissue source and handling, recipient category, transplant technique and site, and recipient treatment protocols.
7. 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, recipient treatment, and post-transplant events.
8. To communicate comprehensive and current information on islet/beta cell transplantation to transplant institutions, the diabetes and general health care community, and the interested general public via the CITR web site (http://www.citregistry.org) publications and presentations.
9. To stimulate prospective and retrospective studies on emerging issues of importance.

1.4 Components of the Registry

The domains of the CITR Registry include:

CUITD: recipients of allogeneic transplant

AUTOG: recipients of autologous islet transplant

CIT: participants in the Clinical Islet Transplant Consortium, Coordinated by the University of Iowa, with which CITR-CC maintains a data sharing agreement under the oversight of the common sponsor, the NIDDK

PCTMY: Total or partial pancreatectomy without subsequent auto or allo islet transplant

XENOG: Xeno-transplantation into human recipient from approved non-human islet sources

ISLPR: donors/islets for any of the above, and any non-clinical human islets approved by the NIDDK to reside in CITR

T1DWL: Type 1 diabetes waiting list for islet transplantation, a comparator group

The CITR Registry is that partition of the CITR Unified Islet Transplant Database (CUITD) inclusive of donor, islet and recipient data from *consenting* recipients of islet allograft, islet autograft and islet xenograft transplantation, as well as total or partial pancreatectomy without autograft. Each domain is fully defined by its own set of case report forms and procedures for data reporting (see the latest version of the Quick

Reference Guide for Allografts and Quick Reference Guide for Autografts, available at www.citregistry.org). For the allograft domain, donor information is required which is made available for the US centers through data sharing agreements with United Network for Organ Sharing (UNOS). Islet recuperation and processing data are also required for each infusion. Additional details are also available in the respective Quick Reference Guides.

1.4.1 The Unified Islet Transplant Database

As of 2009, the Collaborative Islet Transplant Registry provides a repository for any and all islet recovery, isolation, and transplant data related to human islet recipients, via the mechanism of the Unified Islet Transplant Database (CITR/UITD), a superset of the CITR database. These data may include allogeneic or autologous human-to-human, or xenogeneic porcine-to-human donor, islet and recipient data, and approved comparator study groups such as T1D on the waiting list or pancreatectomies without autograft. No other kind of data is permitted in either CITR or UITD.

1.4.2 CITR Consent and use of the data

Recipients giving consent for their data to be included in CITR may have their de-identified data included in any CITR report. No identified data will be used at any time in either CITR or UITD. Recipients not providing consent for their data to be included in CITR will only be included in data files that are accessible only by authorized site users of the EMMES Advantage EDC ® system, the data management system for CITR/UITD, operated by the EMMES Corporation under the main contract for CITR with the NIDDK. Non-CITR UITD data will be used for no purpose other than the site's own needs. Authorized site users of their own site data in UITD will have the ability to download summary reports as well as data files of recipient, donor and islet data for their local use at any time. Use of these downloaded files will be under the individual site's IRB oversight; neither EMMES nor NIDDK assume any responsibility for how the downloaded files are used.

1.4.3 Site and participation eligibility

Requirements for participation are overseen by the CITR Coordinating Center to ensure that participating islet transplant centers comply with Good Clinical Practice regarding data collection and submission. Participating transplant centers must provide annual documentation of adherence to their local Institutional Review or Ethics Board requirements for participating in this endeavor. United States (US) centers must assure compliance with the Health Insurance Portability and Accountability Act (HIPAA).

CITR oversees no specific investigational research protocols, hence bears no regulatory responsibility with respect to allogeneic islet transplantation. As a registry, the requirements for patient enrollment and participation are that the patient has received one or more infusions of islets and that the individual patient's informed consent/assent or a waiver of consent for contributing data to CITR has

been obtained per the site's institutional review board and/or country's oversight body for human research.

1.4.4 Data auditing

Only CITR data (islet transplants or pancreatectomies with recipient consent for inclusion in CITR) will be audited, as stipulated in the main CITR contract with NIDDK.

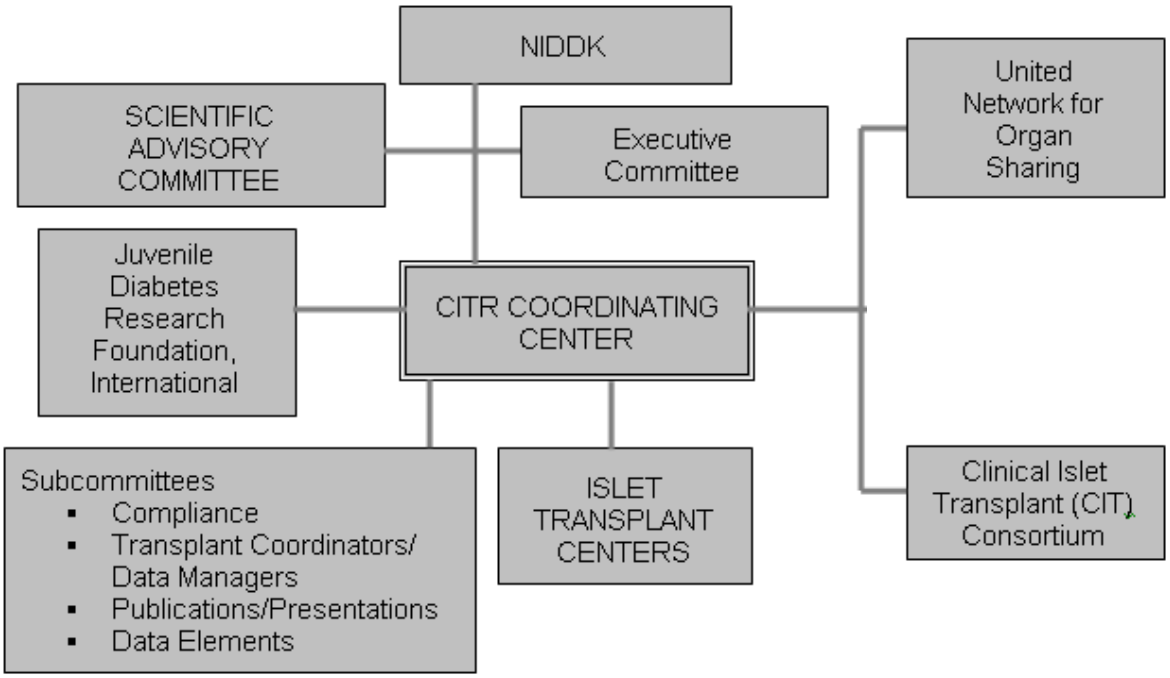
1.4.5 Reimbursements for data reporting

CITR may provide reimbursements for reported data to US and JDRF sites, but not beyond the NIDDK scope of the Registry, nor for data above and beyond the study schedule, even though sites may utilize the CUITD to reposit any and all of their islet transplant data.

1.5 Registry Procedures

1.5.1 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. Below is the operational organization of CITR.



1.5.2 Meetings

An annual meeting of the CITR organization is held at a time and place determined by the Executive Committee. NIDDK or the SAC Chair may call additional meetings, if required.

1.5.3 Site recruitment and membership

CITR recruits the participation of islet transplant centers who then have responsibility for enrolling recipients and collecting follow-up information. Cooperative agreements for data sharing are in place with the United Network for Organ Sharing and with the Islet Cell Resource Centers' Administrative and Bioinformatics Coordinating Center.

Participating transplant centers submit data on procedures relative to any CITR domain 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.

1.5.4 Officers

1.5.4.1 Scientific Advisory Committee (formally the External Executive Committee per the Collaborative Agreement of the NIDDK)

This committee is 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 EEC. The SAC has oversight responsibilities as the CITR Medical Director. The SAC is responsible for the scientific integrity of the Registry. SAC voting members represent the University of Minnesota, the University of Miami, University of California-Los Angeles, the National Institute of Diabetes and Digestive and Kidney Diseases, the United Network for Organ Sharing and the Coordinating Center, and others that may be appointed by the Coordinating Center in consultation with the NIDDK. Non-voting members include representatives of the Juvenile Diabetes Research Foundation International, the National Institute of Allergy and Infectious Diseases , the United States Food and Drug Administration, Centers for Medicare and Medicaid Services , the Canadian Organ Replacement Register, and the CITR Transplant Coordinators'/Data Managers' Committee Chair.

The SAC Chair presides at the study-wide annual meeting, is responsible for overseeing the final annual meeting agenda and serves as an official representative of the Organization.

1.5.4.2 Executive Committee

This committee is comprised of the Project Officer from NIDDK, the SAC Chair and Medical Director, and the Director/Principal Investigator of the Coordinating Center and current and former Chairs of the Publications & Presentations Committee. This Committee meets monthly to ensure that policies pertaining to the Registry are implemented in an organized and consistent manner. They will also oversee the routine operations of the CITR, answer Registry specific questions, and coordinate aspects of the Registry with the SAC.

1.5.5 Standing Committees

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. The Coordinating Center maintains a log of all analysis proposals submitted, approved, published, presented and in progress. All CITR member site Principal Investigators are eligible to submit proposals for analysis toward publication, volunteer to review developing results and co-author on-going analysis efforts.

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.

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.

Data Elements Committee: This 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 volunteer, be elected or be nominated 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 protocol/Manual of Operations may be amended by proposed changes in writing submitted by the Coordinating Center to the Scientific Advisory Committee Chair, and on approval of the NIDDK. Proposed changes can be discussed with the CITR-CC PI, Study Chair and/or NIDDK Scientific officer.

1.6 Registration of Participants/Study Subjects

Islet transplant recipients or identified comparator group cases are registered in CITR by the transplant center once the patient has received an islet transplant or otherwise qualifies for registration, and provides 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 may register the patient in the T1D WL protocol as a comparator case, until they receive a transplant. A person having undergone pancreatectomy without autologous transplant may be registered and followed in the 'PCTMY' protocol of the CITR database. Active or historical subject consent must be obtained as described above. 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 AdvantageEDC℠ User's Guide.

1.7 CITR Data Collection, Use, and Sharing

Donor Data: For transplants performed in the US, donor data is uploaded into the Registry on a regular schedule through data a sharing agreement between the United Network for Organ Sharing and the CITR-CC. This information is continuously checked for consistency between the two databases as it may be edited by either group. The information is then linked to the islet preparation and the recipient data at the time of analysis. For data originating outside the US, various methods to upload or otherwise transfer historical data to the CITR database may be implemented by agreement between the participating site and the CITR-CC.

Islet Data: Since 2009, islet data is reported by the islet processing sites directly to CITR via the CITR data web portal (EMMES Advantage ECD®) or via data uploads according to specified procedures worked out between the site and the CITR-CC. [From 1999 through 2009 in the US, the Islet Cell Resource Centers (ICR) process donated pancreata to isolate and purify transplantable islets. They reported the results to the Administrative and Bioinformatics Coordinating Center (City of Hope National Medical Center, Duarte, CA), who then transfer them to the CITR database on a specified schedule through data sharing agreements with the CITR-CC].

Recipient Data: Certain medical information is collected as part of an islet recipient's transplant procedure(s) and continuing care, and may be entered into the CITR database with the recipient's knowledge and consent. Recipients may withdraw their consent to have their data reported to CITR for any reason at any time, but are strongly encouraged to continue consenting to the inclusion of their data through long-term follow-up, including data capture by telephone interview, mail, or whatever means is agreeable to both the recipient and the participating site. Both short-term and long-term follow-up are vital to the overall success of the Registry. Even in the face of loss of islet function or return to insulin dependence, continued reporting of follow-up data – especially hypoglycemic events, serious adverse events and kidney function -- will help answer important questions regarding any long-term effects.

Abstraction of historical islet recipient information (based on medical care given prior to the site's participation in CITR) may proceed when the local IRB or equivalent body grants a waiver on the basis that the subject is no longer available to give consent for follow-up in real time. Such reports are considered chart reviews and may be included in the CITR Registry, with the local IRB's approval.

Recipients may self-report follow-up outcomes data including adverse events on-line at www.citregistry.org and clicking on "Recipients: Report Your Data". The data will be

collected in a data base separate from the CITR database. It is sent to the site for verification before being uploaded to the CITR database.

CITR data sources, uses and sharing: Data on islet recipients are generally abstracted from the medical record by the participating transplant centers or self-reported by the participants and may be entered into EMMES Corporation's secure, password-protected Internet data entry system, via internet data entry screens located on the CITR password-protected website. Data residing in an electronic database at the site prior to a site's activation in CITR may be uploaded electronically from the center to the EMMES system, after the CITR-CC staff put procedures in place and complete appropriate data mapping. The CITR database comprises an electronic copy of the original data in the respective participating institutions. The aggregate CITR data is available for use by the CITR investigators through the Annual Reports and special focus topics approved by the Publications and Presentations Committee. Individual transplant centers may publish findings based on their own data available to them locally, or by downloading it from the CITR website (available anytime). While the Coordinating Center implements procedures to assure the completeness and quality of the data, the site is solely responsible for the quality of their data. Other researchers who have a need for information from the CITR database may submit an analysis request which is reviewed by the P&P. the data analysis may be conducted by the Coordinating Center and shared with the requesting researchers, or with approval by the P&P Committee, a de-identified summary data file may be transmitted to the site for analysis and manuscript/presentation development, with final review by the CITR P&P Committee.. At the end of the term of operation of the registry and from time to time as may be requested by the sponsor, a copy of the database will be delivered to the NIDDK for archival and/or further analysis. No site-specific analyses will be conducted.

Data collection will terminate when:

1. The term of operation of the Registry under the NIDDK contract ends.
2. An individual islet transplant recipient withdraws consent for further data reporting, or dies.
3. Care of the islet transplant recipient is transferred to a non-participating transplant center.

1.8 Registration

Islet transplant recipients or identified comparator group cases are registered in CITR by the transplant center or by CITR-CC staff by agreement with the respective Clinical Site, once the patient qualifies for registration under one of CITR's domains.

1.9 Informed Consent

Recipients actively transplanted and/or followed by a Clinical Site must provide informed consent for participation in CITR. If a patient has been evaluated and listed for an islet cell infusion, the center may register the patient in the T1DWL protocol as a

comparator case; their follow-up while wait-listed will serve as a useful comparator group. A person having undergone pancreatectomy without autologous transplant may be registered and followed in the 'PCTMY' protocol of the CITR database. Active subject consent or historical (i.e., chart review) IRB waiver must be obtained. Sites may register historical data for islet transplant recipients who have subsequently been lost to follow-up, if their local IRB approves the abstraction of data from the medical record as a chart review. 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, and/or any medical, insurance or government-issued personal identifier. Detailed instructions for data entry are found in the CITR AdvantageEDC℠ User's Guide.

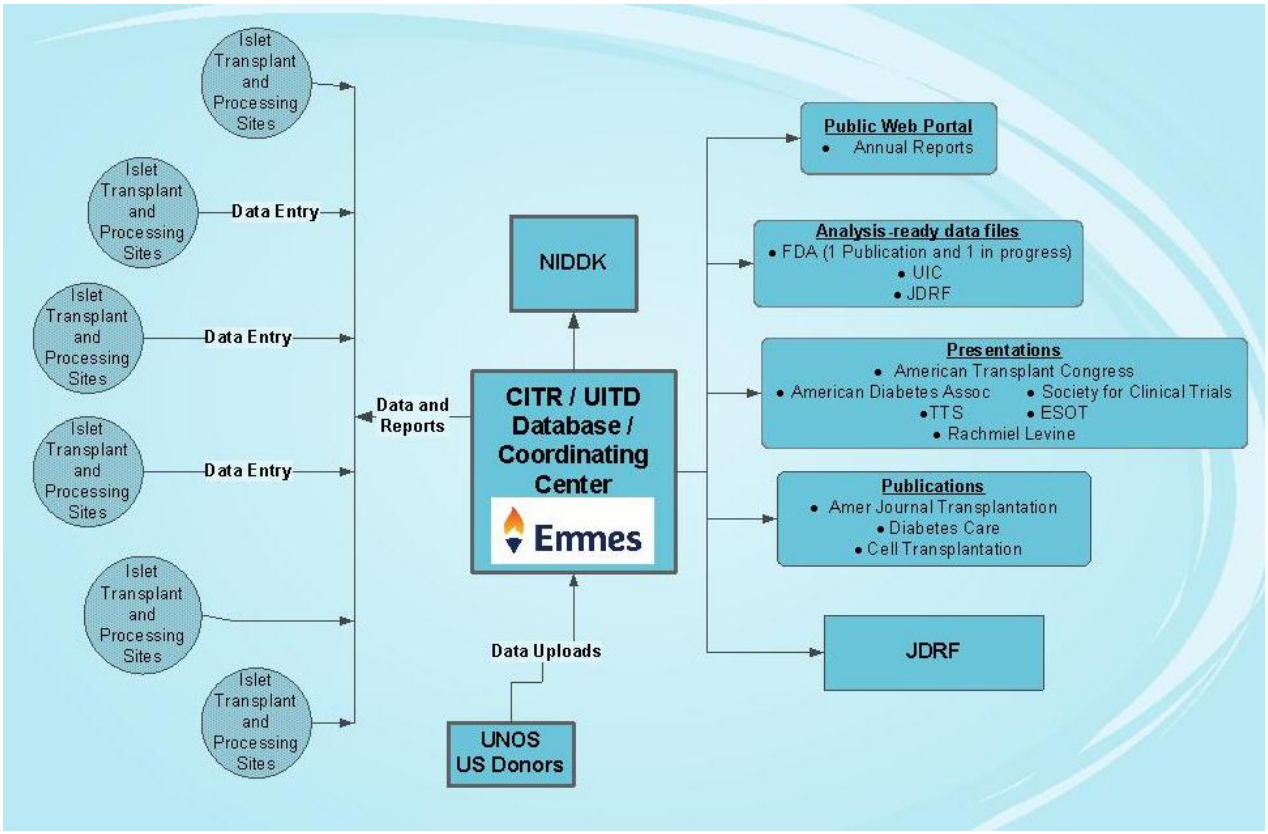
1.10 Follow-up of Registered Participants (Follow-up Schedule)

The required follow-up time points for each registered participant are at baseline, day 28, day 75, six months and twelve months post first islet infusion, regardless of re-infusion. Then post each subsequent infusion, the schedule is re-set and follow-up expected based on the re-infusion date(s). The data submission window period for CITR required time points are as follows:

Baseline:	-180 days to transplant	Year 11:	10 ½ -11 ½ years
Day 28:	14 to 60 days	Year 12:	11 ½ -12 ½ years
Day 75:	60 to 120 days	Year 13:	12 ½ -13 ½ years
Month 6:	120-270 days	Year 14:	13 ½ -14 ½ years
Year 1:	270-540 days	Year 15:	14 ½ -15 ½ years
Year 2:	540-900 days	Year 16:	15 ½ -16 ½ years
Year 8:	7 ½ -8 ½ years	Year 17:	16 ½ -17 ½ years
Year 9:	8 ½ -9 ½ years	Year 18:	17 ½ -18 ½ years
Year 10:	9 ½ -10 ½ years		

See also CITR User's Guide in Secured Access section of www.CITRegistry.org; (see also the Appendix for CITR data elements). The final follow-up schedule is based on the participants' last infusion date. Data can also be submitted at any other time point, but they are not a CITR requirement.

The following chart depicts the flow of data from data sources to the CITR Registry.



2.0 PROJECT ORGANIZATION

CITR is financially supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and has historically received supplemental funding from the Juvenile Diabetes Research Foundation International (JDRF). 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.

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:

1. Vouch for the scientific validity of data on islet preparations, donors and islet transplant recipients entered into the Registry.
2. Direct the activities of the CITR personnel in the transplant center.
3. Coordinate the scientific and administrative operations of the transplant center.
4. Ensure adherence by the CITR personnel to the procedures described in and required by the CITR Manual of Procedures and the AdvantageEDC^{SM} User's Guide.
5. Represent the transplant center at CITR meetings.
6. Participate in CITR initiation visit and data audits by the Coordinating Center.
7. 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:

1. Ensure that potential CITR participants receive appropriate information about the Registry, including the Informed Consent/Assent process and statements (if applicable).
2. Ensure that potential participants have the opportunity to ask questions about CITR. Register participants via the Registry System (AdvantageEDC^{SM}). 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).
3. Maintain a current transplant center roster of Center personnel, address, telephone number(s), and notify the Coordinating Center of any changes.
4. Maintain a file of correspondence with the Coordinating Center.

5. Obtain necessary information on both deceased participants (e.g., date and primary cause of death) and lost to follow up participants (e.g. last known date and type of contact).
6. Review updates of the CITR Manual of Procedures/Protocol, AdvantageEDC^{SM} System and User's Guide and Registry memorandums posted on the CITR Internet.
7. Check completed data screens for accuracy and completeness.
8. Ensure timely transmission of data to the Coordinating Center.
9. Respond to data queries from the Coordinating Center in a timely fashion.
10. Report irregularities or problems to the PI and to the Coordinating Center that can affect the quality of the data collected.
11. Participate in CITR initiation visits and data audits by the Coordinating Center.
12. Represent the transplant center at CITR meetings and during conference calls.
13. Obtain passwords for the CITR web site and frequently review CITR activity.
14. Provide data entry.

2.2 Coordinating Center

The CITR Coordinating Center (CITR-CC), located at The EMMES Corporation, Rockville, Maryland, is responsible for developing and updating the Protocol/Manual of Procedures and AdvantageEDCSM User's Guide, collecting and analyzing registry data, ensuring that the provisions of the Protocol/Manual of Procedures are carried out by all participating transplant centers and coordinating Registry activities. EMMES is renowned for its secure, internet-based suite of data management tools for biomedical research that meet the standards for 21 CFR compliance. EMMES employs a series of corporate standard operating procedures (SOP) that continue to meet the standards set by the US Food and Drug Administration for Good Clinical Practice. Corporate SOPs are tailored to the specific requirements of each project – the requirements of a Registry are different from those of a Phase III randomized clinical trial. EMMES employees are trained to adhere to corporate and project SOPs at all times. 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:

1. Collaborate with other investigators in developing and updating Registry procedures, case report forms, protocol specific user guide instructions, the Manual of Procedures/Protocol, and the AdvantageEDC^{SM} User's Guide.
2. Coordinate and conduct center initiation visits, as well as interim data audit visits and site close out visits.
3. Coordinate communications among the transplant centers.
4. Monitor for adverse events reported by the transplant centers and distribute electronically the pertinent information to participating transplant centers in a timely manner.
5. Review all data entered into AdvantageEDC^{SM} by the sites for completeness and accuracy.
6. Distribute data discrepancy reports to the transplant centers.
7. Create and maintain computerized data files of CITR data.
8. Prepare and distribute Annual Reports and bi-annual updates to the transplant centers.
9. Prepare and distribute monthly accrual and adverse event reports to the transplant centers, SAC and NIDDK.
10. Periodically analyze the frequency of specified events and report to the Scientific Advisory Committee.
11. Prepare recruitment, technical and statistical reports for meetings.
12. Assist in preparing scientific reports for publication and presentation.
13. Distribute periodic data compliance reports to the transplant centers.
14. 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 communication 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.

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

1. Determine optimal meeting dates.
2. Communicate information about meetings to the relevant Committee Chair(s) and meeting participants.
3. Provide logistical support during meetings.
4. Prepare and distribute materials prior to each meeting.
5. Prepare and distribute minutes of the meetings.
6. Follow-up on all action items after each meeting.
7. Coordinate conference calls.
8. The Coordinating Center supports the preparation, duplication and dissemination of administrative and technical reports and manuscripts. These documents include:
9. Protocol/Manual of Procedures
10. Transplant center application materials
11. AdvantageEDC^{SM} User's Guide/protocol specific case report form user guides
12. Meeting minutes
13. Newsletter
14. Statistical reports
15. Bibliographies
16. Abstracts
17. Manuscripts for publication
18. Slides for presentations
19. Roster of CITR personnel

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

1. Compile and organize materials.
2. Coordinate reviews and incorporate comments.
3. Summarize background materials.
4. Write administrative reports.
5. Edit technical language to accommodate lay readers.
6. 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 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 may be scheduled. Upon the completion of all site initiation requirements, 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 Leadership Roster
- Transplant Center Application Information Sheet
- Transplant Center Registration Flow Chart
- Transplant Center Registration Form
- Islet Transplant Summary Form
- Letter of Agreement
- Payment Information Form

- Sample Consent Form
- CITR Protocol/Manual of Operations
- 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 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/admnsimp/, http://www.nchica.org, http://www.amc-hipaa.org/ and http://irb.mc.duke.edu.

3.1.5 CITR Payment System

Letters of Agreement signed by the Coordinating Center and individual CITR clinical sites may specify the payment schedules for contribution of data to the Registry. Stipends for travel to the CITR Annual meeting may be provided by the contract

though the Coordinating Center. There is no further responsibility for any costs, services or activities of the Participating Center.

3.2 Adherence to Protocol/ Manual of Procedures

The CITR Executive Committee approves every Version of this Protocol/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 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 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. No Registry patient or donor will be identified personally as the CITR-CC maintains no personal identifiers (this includes name, address, telephone numbers, affiliations, or any similar information). A participant's data are identified by a unique code known to the site data manager and to the Coordinating Center. All dates are converted in analysis files to time from first transplant. Islet preparation data is linked to the recipient by another code known only to the ABCC and the CITR-CC. Donor information is linked to the recipient by another code known only to the UNOS and the CITR-CC. Final files delivered to the sponsor are stripped of the identifying codes. In addition, the collective CITR 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 Privacy Act

NIH is the primary agency of the Federal government charged with the conduct and support of biomedical and behavioral research. NIH derives its statutory authority from the Public Health Service Act of 1944, as amended numerous times in the last half century (42 U.S.C. 201-300gg). Section 301 of the PHS Act grants the Secretary of DHHS broad permanent authority to conduct and sponsor research. In addition, Title IV authorizes in greater detail various responsibilities, activities, and functions of the NIH Director and the Institutes.

CITR is carried out under a contract from NIDDK to The EMMES Corporation (Contractor). The procurement action requires the Contractor to design, develop, and operate a system of records on individuals to accomplish an agency function in accordance with the Privacy Act of 1974, Public Law 93-579, December 31, 1974 (5 U.S.C. 552a) and applicable agency regulations. The Privacy Act System of Records applicable to this project is Number 09-25-0170. The Contractor is in full compliance with this Act.

3.6 CITR Data Ownership

Registry data constitutes 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.

3.7 Scientific Publications and Presentations

3.7.1 Organization

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

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

3.7.2 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:

1. Maintain a Statistical Analysis Plan for conducting all analysis and writing reports (including the CITR Annual Report).
2. Establish priorities and timelines for data analysis.
3. Identify issues, hypotheses and concepts to be addressed in CITR reports.
4. Invite suggestions for additional analyses from CITR investigators.

5. Identify, propose, and appoint members and chairs of writing teams for developing specific CITR Reports, as necessary.
6. 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:

1. 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.
2. 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.
3. Review activities and progress of writing teams.

3.7.3 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:

1. State the objective(s) of the research/analyses.
2. Identify the specific items in the CITR database, by form name and question number that would be applicable to address each objective.
3. Provide the name, date and location of the meeting, or the intended journal or book for publication.
4. 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.

3.7.4 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 according to recommendations of the Publication and Presentation Committee. Secondary reports will be authored by the principal investigator(s) initiating the analyses and/or the transplant coordinator(s), coordinating center statistician(s) performing the analyses, and “The CITR Research Group.” Limited datasets can also be distributed for CITR sites to help with analysis and manuscript development in the hands of biostatistics/epidemiology faculty or graduate students under faculty supervision.

Any participating transplant center may question authorship of a CITR publication. Such questions will first 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 is complete. Missing information can bias the analysis of Registry data. When data is 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 cannot 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.
- Inform/encourage the participants to submit their data directly to CITR via the online data submission tool available at the CITR website.
- 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 in order 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. Reporting this data into 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 regards 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 is 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:

1. Number of islet transplant participants enrolled by transplant center and cumulative totals.
2. Percentage of error-free data forms (e.g. forms without missing data or data anomalies) by individual transplant center and by all transplant centers.
3. Numbers of missed visits by transplant center and visit, and by all transplant centers.
4. 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.

1. Age, sex, race, etc.
2. Medical history.
3. 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 and Data Accessibility by Participating Sites

5.3.1 Annual Reports

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

- Islet recipient characteristics
- Islet donor factors
- Transplant medical management factors
- Islet processing data
- Immunosuppression and concomitant medical therapy
- Rejection
- Graft function
- Adverse events
- Morbidity, mortality and malignancy
- Loss to follow-up
- Multiple islet infusions
- Non islet transplants

5.3.2 Center Specific Reports

Center specific 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 Center Specific Databases

These will be available to each site for download from the CITR website for their own use.

5.3.4 Site-specific Individual Patient Reports

These reports will be available at the CITR website and will be viewable only by the respective site. They will summarize patient laboratory data, medications, clinical outcomes, adverse events and islet data.

5.3.5 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.

6.0 APPENDIX

6.1 Appendix A. CITR Data Entry and Visit Windows Guidance

CITR Time points – Guidance on Required, Supplemental and Overlapping Data points

Purpose: In order to have as complete a source of comparable data as possible for analysis purposes, CITR has required time points for both the Allograft and Autograft Protocols. The database can also accept any other time points into the database that the Site may want to enter. See Figure 1 below for the required time points and associated visit windows for the both the Allograft and Autograft protocols.

Instructions: Data must be entered for all required visits for both aforementioned protocols. In addition to the required visits, supplemental visit data may also be entered. The R equals required, and S equals Supplemental. The database is also able to accept data that is collected shortly before or after a required visit has occurred. In this event, data should be entered under the appropriate required time point followed by the letters of the alphabet. For example, if a user were entering supplemental data for Day 28, (i.e. data that was collected during a visit that occurred a few days before or after the patient was seen for visit D28), the user would enter D28A, with subsequent data record submissions following the same pattern (i.e. A,B, C, D, E, etc.).

Figure 1

Date Continuum	Required/Supplemental Visits	Enter in EDC
-180 to tx	**R**	**BL**
	S	**D01**
	S	**D02**
	S	**D03**
	S	**D04**
	S	**D05**
	S	**D06**
03- 014	**S**	**D07**
	S	**D08**
	S	**D09**
	S	**D10**
	S	**D14**
	S	**D21**
14- M02	**R**	**D28**
	S	**D56**

Date Continuum	Required/Supplemental Visits	Enter in EDC
M2-M4	R	D75
	S	M04
	S	M05
M4-M9	R	M06
	S	M09
M9-M18	R	M12
	S	M15
	S	M18
	S	M21
M18-M30	R	M24
	S	M30
M30-M42	R	M36
	S	M42
M42-M60	R	M48
	S	M54
Y 4 ½ – 5 ½	R	M60
Y 5 ½ - 6 ½	R	Y06
Y 6 ½ - 7 ½	R	Y07
7 ½ - 8 ½	R	Y08
8 ½ - 9 ½	R	Y09
9 ½ - 10 ½	R	Y10
10 ½ - 11 ½	R	Y11
11 ½ - 12 ½	R	Y12
12 ½ - 13 ½	R	Y13
13 ½ - 14 ½	R	Y14
14 ½ - 15 ½	R	Y15
15 ½ - 16 ½	R	Y16
16 ½ - 17 ½	R	Y17
17 ½ - 18 ½	R	Y18
18 ½ - 19 ½	R	Y19
19 ½ - 20 ½	R	Y20

6.2 Appendix B. CITR Allograft Data Elements

	Data element(s)	Units of measure	Priority for Baseline	Priority for Follow-Up
Recipient data	Gender	M, F	1	-
	DOB	Mm/dd/yyyy	1	-
	Race (North America only)		2	-
	Date of infusion(s)		1	1
	Ethnicity	Hispanic or not	2	-
	Employment status	FT, PT, retired, student, unemployed due to Dx, unemployed other reason	2	2
	Days listed	Days	1	-
	Duration diabetes	Years	1	-
	Duration intensive therapy	Years	1	-
	Smoking	Y/N	1	-
	Weight	Kg	1	1
	Height	cm	1	-
	Fasting plasma glucose	mg/dL or equiv	1	1
	Basal C-peptide	Mg/dL	1	1
	HbA1c	%	1	1
	Severe hypoglycemia events	#/year	1	1
	Daily insulin requirement	U/day	1	1
	Medications			
	- Insulin	Start/stop dates, doses	1	1
	- Lipid-lowering	Start/stop dates, doses	1	1
	- Anti-hypertension	Start/stop dates, doses	1	1
	- Anti-hyperglycemics	Start/stop dates, doses	1	1
	- Immunosuppression	Start/stop dates, doses	1	1
	- Cancer therapy	Start/stop dates, doses	1	1
	Labs			
	- Lipids: Total Chol, HDL, LDL, Triglycerides		1	2
	- Serum: AST, ALT, AlkPhos, Bilirubin, Creatinine		1	1
	Complications of diabetes			
	- Peripheral neuropathy	Y/N	1	1
	- Autonomic neuropathy	Y/N	1	1
	- CAD hx	Y/N	1	1
	- CVA hx	Y/N	1	1
	- PVD hx	Y/N	1	1
	- Retinopathy	Y/N	1	1
	- Macular edema	Y/N	1	1

	Data element(s)	Units of measure	Priority for Baseline	Priority for Follow-Up
	- Blood group	A, A2, B, AB, O	1	-
	Autoantibodies			
	- GAD-65		1	1
	- IA-2		1	1
	- Insulin		1	1
	PRA Class I		1	1
	PRA Class II		1	1
	HIV, CMV, HBV, HCV, EBV		1	-
	Complete graft failure (fasting C-peptide<0.3 ng/mL over 3 months with no spontaneous recovery)		-	1
	Re-infusion		-	1
	Adverse events	Defined in Protocol	1	1
	Loss to follow-up			PRN

	Donor/islet data for each donor/pancreas	Units of measure	Priority at each infusion
Each donor	DOB		1
	Race (North America)		1
	Ethnicity (North America)	Hispanic or not	1
	Weight		1
	Height		1
	Donor blood type		1
	Hx hypertension		2
	Hx alcohol		2
	Hx diabetes		2
	Cause of death		1
	Mechanism of death		1
Each donor	Serum: creatinine, BUN, Bili, AST, ALT, lipase. Amylase, blood glucose,		1
	HIV, CMV, HBV, HCV, EBV		1
Procurement of each pancreas	Procurement team related to transplant center?	Y/N	
	Vasopressors used	Y/N	1
	Steroids used	Y/N	1
	Insulin used	Y/N	1
	Transfusions pre-operatively and intra-operatively	Y/N	1
	Date/times of: admission, brain death, cross-clamp, recovery, preservation solution, transport, arrival, digestion		1
	Preservation solution		1
Processing of each pancreas	Processing lab related to transplant center?	Y/N	1
	Collagenase	By name	1
	Thermolysin	Y/N	1
	Pulmozyme	Y/N	1
	Culturing	Y/N, time	1

	Donor/islet data for each donor/pancreas	Units of measure	Priority at each infusion
	Gradient	Type	1
	Microbiology - Gram stain - Aerobic - Anaerobic - Fungal - mycoplasma		1
Final product characteristics, per pancreas	- Total cell volume - Total islet particles - embedded islets (%) - IEQs infused - Beta cells - Insulin content - Endotoxin units - Potency/stimulation index - Purity - DNA		1 1 1 1 1 1 1 1 1 1 1
Cross-match	-		1

6.3 Appendix C. CITR Autograft Data Elements

	Data element(s)	Units of measure	Priority for Baseline	Priority for Follow-Up
Autograft Data	Gender	M, F	1	-
	DOB	Mm/dd/yyyy	1	-
	Race (North America only)		2	-
	Date/time of infusion (s)		1	1
	Ethnicity	Hispanic or not	2	-
	Employment status	FT, PT, retired, student, unemployed due to Dx, unemployed other reason	2	2
	Days listed	Days	1	-
	Duration diabetes	Years	1	-
	Duration intensive therapy	Years	1	-
	Smoking	Y/N	1	-
	Weight	Kg	1	1
	Height	cm	1	-
	Fasting plasma glucose	mg/dL or equiv	1	1
	Basal C-peptide	Mg/dL	1	1
	HbA1c	%	1	1
	Severe hypoglycemia events	#/year	1	1
	Daily insulin requirement	U/day	1	1
	Medications			
	- Insulin	Start/stop dates, doses	1	1
	- Lipid-lowering	Start/stop dates, doses	1	1
	- Anti-hypertension	Start/stop dates, doses	1	1
	- Anti-hyperglycemics	Start/stop dates, doses	1	1
	- Immunosuppression	Start/stop dates, doses	1	1
	- Cancer therapy	Start/stop dates, doses	1	1
	Labs			
	- Lipids: Total Chol, HDL, LDL, Triglycerides		1	2
	- Serum: AST, ALT, AlkPhos, Bilirubin, Creatinine		1	1
	Complications of diabetes			
	- Peripheral neuropathy	Y/N	1	1
	- Autonomic neuropathy	Y/N	1	1
	- CAD hx	Y/N	1	1
	- CVA hx	Y/N	1	1
	- PVD hx	Y/N	1	1
	- Retinopathy	Y/N	1	1
	- Macular edema	Y/N	1	1
	- Blood group	A, A2, B, AB, O	1	-
	Medical History			
	- Prior medical procedures: ERCP (Diagnostic or Treatment), Stents		1	

	Data element(s)	Units of measure	Priority for Baseline	Priority for Follow-Up
	(Plastic, or Metal), Nerve Blockage, Drainage, Enzyme replacement			
	- Prior surgical procedures: Frey, Puestow, Traveral, Whipple, Partial Pancreatectomy		1	
	- Was a pancreatectomy performed	Y/N	1	
	- Date/time hospital admission		1	
	- Date/time of pancreatectomy (if applicable)		1	
	- Duration of cold ischemia		1	
	Islet Processing/Testing			
	- Incubated w/preservation solution to get rid of exocrine	Y/N	1	
	- Collagenase type: Liberase HI, Type IV, Collagenase P, Sigma Blend, NB1, Thermolysin, Collagenase IV, Blendzyme		1	
	- Collagenase types and lot numbers		1	
	- Islet purification (none, density gradient, or other)		1	
	- Total packed cell volume		1	
	- Percent trapped islets		1	
	- Total islet count		1	
	- Time of Islet Equivalent count		1	
	- Total number of Islet Equivalents		1	
	- Total number of beta cells		1	
	- Islet Microbiology results (Gram stain, Aerobic culture, Anaerobic culture, Fungal culture)		1	
	- Total endotoxin units in final preparation		1	
	- Islet Purity (Percent dithizone positive, Percent beta cells)		1	
	- Islet viability		1	

	Data element(s)	Units of measure	Priority for Baseline	Priority for Follow-Up
	Complete graft failure (fasting C-peptide<0.3 ng/mL over 3 months with no spontaneous recovery)		-	1
	Re-infusion (database supports up to 2 tx per participant)		-	1
	Adverse events	Defined in Protocol	1	1
	Loss to follow-up			PRN