



COLLABORATIVE ISLET TRANSPLANT REGISTRY

PROTOCOL

Version 3.0

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**Prepared by
The CITR Coordinating Center**

**The EMMES Corporation
401 North Washington Street, Suite 700
Rockville, MD 20850
www.CITRegistry.org**



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Collaborative Islet Transplant Registry (CITR)

Protocol

I. BACKGROUND AND PURPOSE

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, 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 depends 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.

II. COMPONENTS OF THE REGISTRY

The CITR Registry is that partition of the CITR Unified Islet Transplant Database (CUITD) inclusive of donor, islet and recipient data relating to the CITR-consenting islet allograft and autograft recipients. Each system 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). For the allograft component, donor information is required which is made available for the US centers through data sharing agreements with United Network for Organ Sharing. For both components, islet recuperation and processing data are also required for each infusion. Full details are available in the Manual of Operations and in the respective Quick Reference guides, which are also available at the CITR website.

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.

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 will be accessible only by authorized site users of the EMMES Advantage EDC system, which is 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 site's IRB oversight; neither EMMES nor NIDDK assume any responsibility for how the downloaded files are used.

Data auditing. Only CITR data (human-to-human transplants with recipient consent for inclusion in CITR) will be audited as stipulated in the main CITR contract with NIDDK.

Clinical reimbursements. CITR will not provide any clinical data reimbursements for reported data that is beyond the subcontract requirements of CITR (human-to-human allogeneic or autologous islet transplantation). CITR will provide clinical reimbursements for CITR-stipulated human islet recipient data, according to the terms stipulated elsewhere in the Protocol.

III. SITE AND PARTICIPANT ELIGIBILITY

Requirements for participation are enforced 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 implements and enforces no specific investigational research protocols. As a registry, the requirements for patient enrollment and participation are that the patient has received one or more infusions of human 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.

IV. STUDY ORGANIZATION AND GOVERNANCE

Under its contract with the NIDDK, the *CITR Coordinating Center (CITR-CC)* implements the goals and executes the tasks of the Registry by providing support for logistical issues, data capture, quality control monitoring, site visits to the transplant centers, and statistical design and analyses for reports. The *CITR Scientific Advisory Committee (SAC) Chair* 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, VA Puget Sound Health Care Systems, Uppsala University Hospital (The Nordic Network), the National Institute of Diabetes and Digestive and Kidney Diseases, the United Network for Organ Sharing and the Coordinating Center. Non-voting members include representatives of the Juvenile Diabetes Research Foundation International, the National Institute of Allergy and Infectious Diseases, the National Center for Research Resources, the United States Food and Drug Administration, Centers for Medicare and Medicaid Services, the United States Health Resources and Services Administration, the Canadian Organ Replacement Register, and the CITR Transplant Coordinators'/Data Managers' Committee Chair.

An *Executive Committee*, comprised of the CITR Medical Director, the NIDDK Project Officer and the Coordinating Center Principal Investigator, meets monthly to ensure that policies pertaining to the Registry are implemented in an organized and consistent manner.

Several permanent and ad-hoc subcommittees, comprised of CITR participating site directors and other invited experts as appropriate, help guide the work of the Registry:

- the *Data Elements Committee* recommends which data are to be collected by the Registry and determines application of terminology standards;
- the *Compliance Committee* monitors overall progress and completeness of required data reporting from the participating sites;

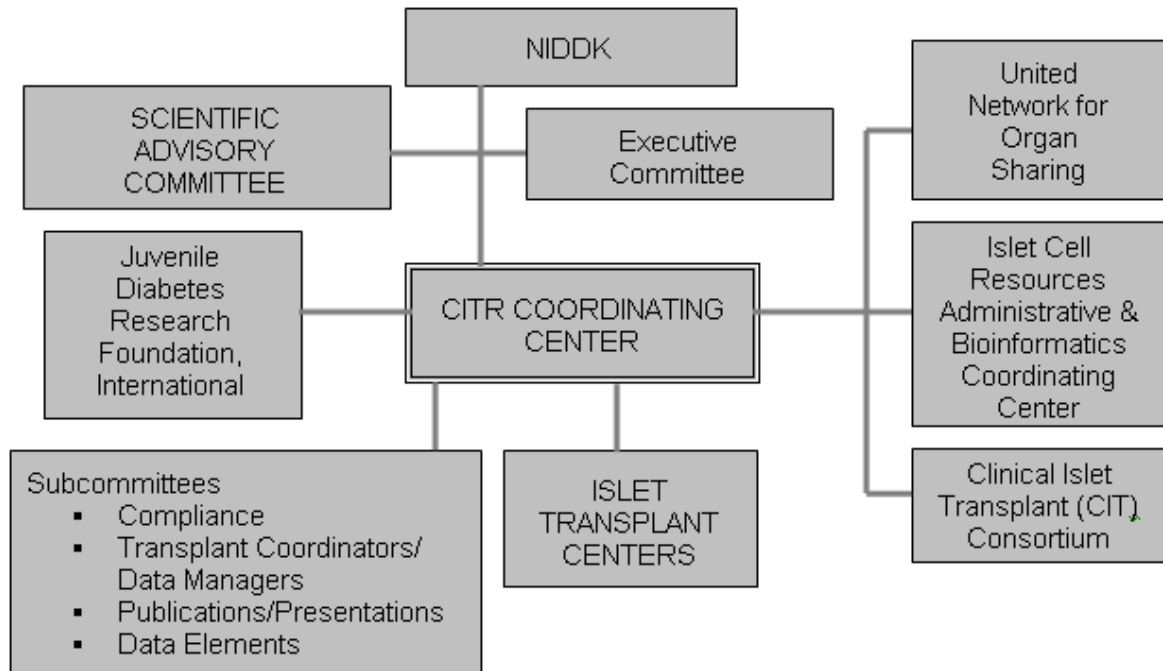
- the *Publications and Presentations Committee* determines analysis priorities, oversees progress in reporting, and reviews and approves the Annual Reports, all manuscripts and presentations;
- the *Transplant Coordinators/Data Managers* group collectively reports and collaborates on the practical aspects of patient follow-up and data reporting.

CITR collaborates in pursuing common goals and in sharing donor and organ data with the United Network for Organ Sharing (UNOS), and with the Administrative and Bioinformatics Center (ABCC) of the City of Hope, which serves as the coordinating center for the Islet Cell Resource Centers, who in turn provide purified islets and islet product characterization for islet transplantation in the US.

Islet transplant centers' voluntary participation in the Registry is effected through Letters of Agreement with the Coordinating Center.

Figure 1 shows the CITR organizational chart.

FIGURE 1: CITR ORGANIZATIONAL CHART



V. 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 and the JDRF-funded European and Australian Centers 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:
 - Safety of islet/beta cell transplant product and procedure and protocol-regulated treatment products.
 - 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.
 - 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.
5. 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.
6. To stimulate prospective and retrospective studies on emerging issues of importance.

VI. METHODS

A. Site Recruitment

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.

B. Data Collection, Use and Sharing (See also Confidentiality.)

1. **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.
2. **Islet data.** In the US, the Islet Cell Resource Centers (ICR) process donated pancreata to isolate and purify transplantable islets. They report 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.
3. **Recipient data.**
 - a. Much medical information is collected as part of an islet recipient's transplant procedure(s) and continuing care, and, if the site is an active CITR participant at the time, is 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 will help answer important questions regarding any long-term effects, as well as help evaluate effects at a more fundamental biologic level.

b. Abstraction of historical islet recipient information (based on medical care given prior to the a 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. Thus, such reports are considered chart reviews and may be included in the CITR Registry, with the local IRB's approval.

c. Recipients may self-report key follow-up outcome data including insulin use and 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.

- 4. CITR data sources, use 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 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 data in whatever form it may be available to them locally, or by downloading it from the CITR website. 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, and in particular, the quality of their data at any point in time. A site's own data is always available for downloading by the site in various common data file formats. Other researchers who have a need for information from the CITR database may submit an analysis request which is approved by the P&P, conducted by the Coordinating Center and shared with the requesting researchers. 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.

CITR data are limited to the responses by living CITR participants or their surrogates (in the case of minors or those unable to respond on their own behalf owing to illness or cognitive impairment). Data cannot be obtained from Next of Kin survivors of deceased patients.

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.

C. Coordinating Center Procedures.

The EMMES Corporation, Rockville MD, (www.emmes.com) serves as the CITR Coordinating Center. 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. The CITR project – like many conducted by The EMMES Corporation – is implemented by a team of specialists in statistics, project management, data management, computer programming, database development and implementation, and administrative coordination, assisted by functional corporate units in information technology, systems coordination and logistic support.

VII. STATISTICAL ANALYSIS

A general plan for the analysis of CITR data is outlined in the CITR Statistical Analysis Plan, which is a formal study document and is available on request from the Coordinating Center. Analyses for CITR include data quality, study progress, and clinical outcomes. A comprehensive Annual Report summarizing data received is made available publicly and issued to each participating transplant center. Database assessments are performed by the Coordinating Center to evaluate data quality on a monthly basis and these reports are distributed to each participating site via a specialized web page. In addition to these planned analyses, the Coordinating Center conducts various unplanned analyses precipitated by evolving registry needs. Requests for such analyses come from the participating investigators and the Scientific Advisory Committee with final approval by the Publications/Presentations Committee.

VIII. PUBLICATION AND DISSEMINATION OF RESULTS

The main vehicle for reporting and disseminating cumulative results of the Registry is the Annual Report, which is drafted and reviewed for final version by the Publications and Presentations Committee and then by the Scientific Advisory Committee. The final report each year is made publicly available, including download from the CITR website. Presentation slides of each report are also available at the website. The Collaborative islet Transplant Registry should be credited whenever CITR results are presented. Salient results may be presented at major meetings on islet transplantation and/or

diabetes, as well as publication in peer-reviewed journals. Focus topics are developed for analysis and submission for publication in peer-reviewed journals. The Publications and Presentations Committee must approve all analysis requests and focus topic for analysis.

IX. CONFIDENTIALITY

A. Patient data

The CITR adheres to standards of Good Clinical Practice that prohibit the identification of any specific individual in the data and any files managed by the CITR Coordinating Center. An individual islet transplant recipient is never identified by any personal identifiers including 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.

B. 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.