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Policies and Procedures for the Islet Cell Resource Centers (ICRs) Consortium

Division of Clinical Research

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POLICY AND PROCEDURES FOR THE ISLET CELL RESOURCE CENTERS (ICRs) CONSORTIUM

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I. GENERAL POLICIES AND PROCEDURES

1.0 STATEMENT OF PURPOSE

The Islet Cell Resource Centers (ICRs), funded by the National Center for Research Resources (NCRR) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), comprise an interactive group of 8 academic laboratories charged with the pursuit of three major goals. The first is to provide pancreatic islets to eligible investigators for use in Food and Drug Administration (FDA)- and Institutional Review Board (IRB)-approved clinical protocols in which isolated human islets are transplanted into qualified patients afflicted with type 1 diabetes mellitus. The ICRs will provide islets for protocols approved by the ICR Steering Committee. The second goal is to optimize the harvest, purification, function, storage and shipment of islets while developing tests that characterize the quality and predict the effectiveness of those islets transplanted into patients with diabetes mellitus. The third goal is to provide pancreatic islets for basic science studies.

2.0 ICR STEERING COMMITTEE

2.1 Function

The ICRs are an interactive group of 8 academic laboratories whose primary purpose is to supply investigators with clinical grade islets for ICR-approved studies. The Steering Committee oversees the general functions of the ICRs based on the present Policy and Procedures document and evaluate the clinical and scientific merit of requests for ICR services.

2.2 Members

The ICR Steering Committee will be composed of: 1) *ad hoc* experts in disciplines relevant to islet transplantation, 2) the principal investigator or authorized delegate of each ICR production facility, 3) representatives of the NCRR, NIDDK, Juvenile Diabetes Research Foundation (JDRF) and FDA, 4) the Administrative and Bioinformatics Coordinating Center (ABCC) Director, and 5) a chairperson. This committee will have a maximum of 17 voting members and, in accordance with the "Cooperative Agreement" mechanism of funding, the National Institutes of Health (NIH) representatives (from the NCRR and NIDDK) will have voting representation on the Committee that will not exceed 40%.

The FDA representative will be a non-voting member of the Steering Committee.

An expert in fields relevant to islet cell transplantation will serve as chairperson of the Steering Committee. The Director of NCRR's Division of Clinical Research (DCR) will select this individual.

The Administrative and Bioinformatics Coordinating Center (ABCC) will organize, record, and generate the complete written minutes of each ICR Steering Committee meeting.

The Steering Committee chairperson may nominate additional individuals as *ex officio*, non-voting observers. These individuals may attend Steering Committee meetings but may not attempt to influence the discussions or decisions of the Steering Committee. The term of service for *ex officio* observers will be one year, subject to approval by the Steering Committee and may be renewed by vote of the Steering Committee.

Each voting member, or their institutional designate, will be permitted to cast a single vote on proposals brought to the Steering Committee. A quorum for conducting an ICR Steering Committee meeting shall consist of a minimum of 10 members, of whom at least five are ICR Directors. A member may be represented by an alternate of his/her choice who will, for that meeting, exercise full committee rights of the absent member.

2.3 Experts

The Steering Committee should include a breadth of expertise relevant to islet cell transplantation, including the clinical and medical specialties most likely to apply this technology in clinical studies. To expand the expertise existing among the ICR Directors, additional experts, not affiliated with an ICR or an ICR institution, should participate as full, voting members of the Steering Committee.

When additional expertise is deemed necessary to address specific items on the ICR Steering Committee agenda, *ad hoc* consultants may be invited by the Committee Chair to participate in the meeting as voting members. Generally such appointments will be on an *ad hoc* or a per meeting basis. It is the prerogative of the Committee Chairperson to appoint a substitute for any outside member absent from an appropriately announced Steering Committee meeting.

2.4 Non-voting Members

The ICR Steering Committee may request the assistance of outside experts drawn from relevant fields, such as ethics and law, on an *ad hoc* basis. These consultants may be drawn from agencies such as the NIH, FDA, and non-ICR institutions.

2.5 Scientific Charge

The primary purpose of ICRs is to provide clinical grade islets for transplantation protocols. The secondary purpose, pursued simultaneously, is to establish additional parameters predictive of their clinical function and to investigate isolation and testing procedures to optimize the number, quality, and clinical utility of harvested islets. Finally, the ICRs will provide islets for basic science studies.

The ICR Steering Committee will evaluate and prioritize clinical transplantation protocols requesting islets based on standard criteria. Priority scores will be assigned based on the NIH Adjective Scale. The ABCC Director is responsible for recording accurate summaries that reflect these scientific reviews.

The Steering Committee will make every effort to have all islets used for therapeutic purposes. The order of priority shall be: (1) transplantation into the primary patient of an ICR Steering Committee-approved clinical protocol, (2) transplantation into a different, but similarly approved patient at the same

institution if the primary patient is unavailable, (3) optimizing and testing islet cell processing procedures, and (4) providing islets for basic laboratory research.

Prior to a Steering Committee meeting, each clinical transplantation application will be reviewed by a minimum of three Steering Committee members (one primary reviewer, one secondary reviewer, one biostatistical reviewer) and an expert in a related field who is not a Steering Committee member (chosen by the Steering Committee chairperson). Their written critiques will be forwarded to the other members of the Steering Committee through the ABCC.

2.6 Appointments

There are no term limits for the Chairperson, NIH representatives, FDA representative, and ICR facility Directors to serve on the Steering Committee. Other experts serving on the Committee will be appointed to two-year terms. In certain situations, outside experts may be appointed for three years, in order that their terms overlap those of future appointees. Outside expert appointments are renewable. *Ad hoc* membership on the Steering Committee will be on a per meeting basis, unless appointed to longer terms by a majority vote of the Steering Committee.

2.7 Meetings

The ICR Steering Committee will meet three times during the first year of funding, and twice per year thereafter. During these meetings, the following topics will be addressed: (1) the production goals for each ICR facility, (2) review of activities of the member facilities, including the number of pancreata obtained and islets generated for both clinical transplantation protocols and basic science studies, description of islet function and correlation with isolation parameters, identification of investigators and their institutions that received islets, and the clinical and laboratory protocols for which they were used, (3) discussion of quality control issues, (4) discussion of progress in all basic science, isolation, testing, shipping, and storage procedures and their validation as clinical correlates, (5) review of applications submitted requesting islets for clinical or basic science use, (6) an update on the clinical protocols approved at previous Steering Committee meetings to include patient enrollment, data submitted, complications, and completion status and (7) an update on basic science islet applications and distribution. The Steering Committee Chairperson may call additional meetings.

The ABCC Director will be charged with generating and distributing an agenda prior to each meeting. The Committee members are encouraged to suggest topics requiring discussion to the Committee Chair at least three weeks prior to each meeting. Any voting Committee member can suggest discussion topics. All motions must be seconded in order to be voted upon. Approval will require a simple majority, with the Chair casting the deciding vote in the case of a tie. Robert's Rules of Order will be followed for discussion of agenda topics, with the exception that the Chair may vote on issues proposed by the Committee.

After consideration of confidentiality and privacy issues and upon approval by the Steering Committee, the ABCC Director will make public, via the ICR Web site or other means, appropriate data, discussions of and decisions made by the Steering Committee. The intent is to share information with the scientific and public

communities as quickly as possible to advance the field, and general understanding, of pancreatic islet transplantation and basic research.

2.8 Executive Committee

The chairperson, the NCRR representative, one additional NIH representative, two non-ICR voting members of the Steering Committee, the ABCC Director, and one ICR Director selected by the Steering Committee will comprise the Executive Committee. Its responsibilities will be administrative in nature, and decisions on major policy issues will not be made. Meetings will be chaired and called by the chairperson of the Steering Committee; meetings may be held by teleconference several times throughout each year. Each member will have one vote, and decisions will be based on a majority vote. The Chairperson will cast the deciding vote in case of a tie. An advance agenda of Executive Committee meetings will be sent to Steering Committee members by e-mail. Deliberations of the Executive Committee will be open to Steering Committee members. Review Composition of the Executive Committee.

2.9 Information Disclosure Policy

Participation in the ICR in the ICR Consortium is based on the principle of sharing knowledge to further the ICR objective to optimize the "harvest, purification, function, storage and shipment of islets". Withholding intellectual property undermines the mission of the ICR and may deter the free sharing of critical information by ICR participants. Thus ICR Members should freely divulge detailed information related to islet cell optimization methodology, under the following assurances:

- Shared information among participating ICRs shall not preclude the protection of intellectual property or the filing of patent opportunities for ICR members.
- Appropriate confidentiality must be implemented for products that are not yet patented or for information that is not yet in the public domain. ICRs shall not discourage the development of new inventions and/or the formation of business entities to commercialize components of cell processing technology.

3.0 ADVERTISING OF ICR RESOURCES

The services of the ICR will be advertised in scientific journals as a means of soliciting islet requests. When possible, additional advertisements will be included in NIH publications, on the Internet, and at scientific meetings.

4.0 ASSIGNING PRODUCTION PRIORITIES FOR CLINICAL PROTOCOLS

4.1 Determining Priority Scores

All applications requiring full ICR review, i.e. administrative and scientific, will be discussed at the Steering Committee meeting and receive a priority score using the NIH adjectival scale. The categories are Outstanding (1-1.5), Excellent (1.5-2.0), Very Good (2.0-2.5), Good (2.5-3.5), Acceptable (3.5-5.0), and Not Recommended for Consideration. Each proposal will be evaluated for:

1. Quality of Preliminary Data

2. Clinical Relevance
3. Feasibility
4. Protocol Design
5. Originality
6. Overall Scientific Merit

4.2 Modifications in the Proposed Protocols

The Steering Committee can require modifications in islet preparation and clinical approaches as a condition for use of ICR resources. Such recommendations will be made when the Steering Committee believes the modifications will significantly improve the likelihood of accomplishing the proposed objectives or the safety or feasibility of the application.

4.3 Recommendations for Support

The Steering Committee will base its recommendation for ICR support on the above considerations (part 1, section 4.1). Each proposal will be placed in one of the following categories:

Recommended for Support - The committee determines that the scientific merit warrants islet generation, and the ICR has the capacity to meet the study needs.

Recommended for Support Contingent on Modifications - The committee judges that the scientific merit of the request warrants support that can be provided by the ICR. However, the committee suggests that certain modifications be made in the request. The investigator must respond to the suggested modifications. The response will be addressed to the ABCC Director who will then distribute it to the reviewers. If the reviewers are satisfied with the investigator's response, the application can be recommended for support to the Steering Committee Chair who will make the final decision with the NCRR representative. If a reviewer, the Steering Committee Chair, or the NCRR representative is not satisfied with the investigator's response, the response will be discussed with the full Steering Committee to determine the disposition of the application.

Alternate Status - The proposal is of meritorious quality but due to insufficient ICR resources or scheduling conflicts, its needs cannot be met. However, if resources become available before the next Steering Committee meeting, an ICR will attempt to generate the requested islets. The investigator is not required to resubmit the protocol, but if islets have not been generated by the time of the next meeting, the investigator can request that it be placed in competition with the new applications and rescored.

The purpose of the Alternate Status is to identify proposals which are of high scientific merit but were not placed in "Recommended for Support" status due to limitations in the available ICR resources. Upon request of the applicant, such proposals will be considered for reprioritization at the next Steering Committee meeting. The investigator may also submit additional information prior to that meeting. Proposals in the Alternate Status category may be reclassified to "Recommended for Support" status if another proposal that had been recommended is withdrawn or fails to respond satisfactorily to suggested modifications or fails to comply with ICR guidelines. Replacement of a previously recommended proposal by one in Alternate Status will be based on priority scores

and the availability of resources. A majority of the Steering Committee members must approve such a change in status.

Deferral - The reviewers judge the proposal to be of scientific merit but containing insufficient data to warrant support. Investigators may resubmit a revised proposal to the ABCC for forwarding to the Steering Committee. At the discretion of the Steering Committee, recommendations may be made prior to its next meeting, or the application may be held for discussion at the next meeting. If a previously deferred application is deferred a second time, the application will not be reconsidered unless it is resubmitted as a new application.

Not Recommended For Support – The Steering Committee determines that ICR support is not warranted. The application may be resubmitted to the next meeting if significant changes in response to the reviews have been made.

Applicants may respond to having their application placed in any of these classifications by writing to the ABCC Director. Such responses will be considered at the next ICR Steering Committee meeting.

4.4 Notification to Investigators

The written critiques submitted by the reviewers will be sent to the investigators. The investigator will also be notified in writing of the ICR Steering Committee recommendations.

5.0 ABCC RESPONSIBILITIES

5.1 ICR Steering Committee Meetings

The ABCC will be responsible for organizing the ICR Steering Committee meeting. Dates will be set to maximize the attendance of committee members. Non-Federal voting members invited to such meetings may be reimbursed for travel expenses through their own ICR cooperative agreement or that of the ABCC. The ABCC will be responsible for arranging the meeting location and for distributing the agenda and review materials at least two weeks prior to the meeting. The ABCC will maintain audio-records and written minutes.

5.2 Review of Requests for ICR Resources

The ABCC Director will organize the review process. The “Application for ICR Resources” and assistance in application procedures will be provided by the ABCC. Additional ABCC duties include receipt of applications and their assignment to ICR Steering Committee reviewers with appropriate expertise, distribution of applications to other Steering Committee members, collation of reviews and Steering Committee findings, and communication of Steering Committee decisions to the applicant. One copy of “Application for ICR Resources” applications and all related documents will be kept on file at the ABCC.

5.3 Maintenance of Databases

The ABCC will maintain databases as specified by the Steering Committee in a manner that is accessible through an ICR home page. The databases will be comprised of information submitted by ICR Directors and ICR-supported

investigators in the format determined by the ABCC. The information will be made available electronically through the ICR home page to facilitate the design of subsequent studies. The ABCC has established both a Web site that is restricted to Steering Committee members and a Web site that is accessible to the public. The ABCC will facilitate contact between investigators and ICR production facilities, acknowledging that information will remain confidential and not be entered into databases until the Steering Committee has given approval to do so.

The ABCC will receive, collate, and analyze all relevant data resulting from all protocols that use ICR resources. These data and analyses will be discussed at each Steering Committee meeting and used to design prospective studies that will establish parameters that predict the clinical utility of any batch of islets.

5.4 Collaborative Studies

The ABCC will be responsible for organizing collaborative studies within the ICR. The ABCC will establish appropriate committees in concert with the ICR Chairman and Executive Committee to review collaborative studies, schedule conference calls, and provide meeting agendas and minutes. The ABCC will collect and analyze data from these studies as needed. The ABCC will ensure that final study reports are submitted to NIH for these collaborative efforts. The ABCC will provide project funding from NIH ICR restricted funds for these studies, if approved by the Steering Committee.

6.0 CONFLICT OF INTEREST

Efforts will be made to avoid conflict of interest or the appearance of conflict of interest by members of the Steering Committee. Members must not be present during discussion and may not vote on any “Application for ICR Resources” which (1) is submitted by faculty from the member's institution; (2) is submitted by an investigator with an ongoing or prior collaboration within the previous six months; or (3) if the ICR Steering Committee member has a financial or fiduciary interest in either the organization or the protocol for which islets are requested.

Members of the Steering Committee will be required to sign a conflict of interest and financial disclosure statement yearly and at the time of each Steering Committee meeting indicating any financial or fiduciary interest related to the applications under consideration. Investigators will also be required to disclose any such interests in the application being submitted. These documents will be provided and maintained by the ABCC.

7.0 AUTHORSHIP ISSUES

The ICRs are NIH-sponsored service facilities. Members of the ICR will not expect authorship on investigator publications if islet generation was the only contribution. Investigators will be required to acknowledge the ICR in all publications, in the same manner that funding support is acknowledged.

The ICR Publication Committee developed a Publication Policy. This Committee is comprised of Steering Committee members, the ABCC support scientist, and technical staff from various islet centers. Briefly, the publication policy requires all investigators wishing to access ICR data to submit a Concept Template that will be reviewed by the Publication Committee prior to using ICR data. If approval is given by the Publication Committee, an investigator can request that islet data be analyzed by the ABCC on behalf of the authors. No data will be directly transferred to an investigator. When an investigator wishes to write an abstract or article using ICR data, the ABCC will send the approved Concept Template with a call for authorship to the entire Steering Committee membership. If an investigator would like to participate in co-authoring the publication, he/she will submit their name to the Publication Committee for consideration. If this is agreeable with the primary author, they will be included in the publication development. If the primary author does not consider the input of the Steering Committee member of value to the publication, he/she may object, in which case the primary author and chair of the Publication Committee will resolve the issue. The JAMA rules for co-authorship will be used to determine authorship participation.

ISLETS FOR CLINICAL TRANSPLANTATION PROTOCOLS

8.0 ELIGIBILITY REQUIREMENTS

To be eligible to receive ICR islets for clinical transplantation protocols, an investigator must: (1) be employed by and perform the proposed study within a U.S. domestic institution or government agency and also have the expertise to perform the proposed clinical and scientific studies, (2) submit a request for ICR-generated islets as described in part II-Section 2.0, 3.0 and 4.0, using form PHS 398 (rev. 5/01), (3) agree to post-distribution monitoring as defined in part II-Section 10.0, (4) follow the guidelines of the NIH, FDA, and the local Institutional Biosafety Committee (IBC), Institutional Review Board (IRB) and the current ICR Policy and Procedures document (version February 2006), (5) agree to assurance and certification requirements as described in the Application for a Public Health Service Grant (PHS 398 Section III.G), (6) agree to maintain the confidentiality of any pre-clinical or clinical information furnished by the ICR, (7) agree to permit incorporation of all data derived through the generation or use of ICR-provided islets into both the ICR ABCC databases and the National Institute of Diabetes and Digestive Kidney Diseases (NIDDK)-supported Islet Registry, (8) disclose all other forms of support for this project, private or academic collaborations, and fiduciary relationships relevant to the proposed islets and their clinical use, and (9) cite the ICR support in all resultant publications.

Applicants wishing to use islets for a clinical transplant protocol submitted to, peer-reviewed and funded by the NIH, JDRF, American Diabetes Association (ADA), and/or American Heart Association (AHA) will be subject only to an administrative review by the ABCC in order to ensure that the required documentation in section II, part IV, items 1-8 have all been provided and adequately addressed. These applicants will be informed of their approval status within two weeks of the receipt of their application.

Recommendations of the ICR Steering Committee to ship islets to an investigator whose clinical protocol has not been peer-reviewed and funded by the NIH, JDRF, ADA, and/or AHA will not only undergo an administrative review, but also a scientific review, in order to assess the merit and feasibility of the proposal, including: (1) the clinical and pre-clinical data leading to the proposed clinical trial, (2) the suitability and technical feasibility of the proposed approach, (3) the capacity of the investigator to enroll patients in the proposed study, (4) the availability of the required laboratory support, (5) the planned statistical evaluations of the clinical and laboratory endpoints, (6) the technical, legal, and ethical issues of the proposed protocol, (7) the likelihood of success for the proposed approach in relationship to other clinical trials, (8) the resources required for the proposed trial, including sources of funding for safety testing, clinical studies, data management, and post-therapy laboratory and clinical evaluations, (9) the current status of the proposed protocol, (10) efforts to ensure that NIH guidelines for patient safety, and minority and gender representation in the clinical trial are satisfied, and (11) identification of all sources of support for the project. All such applicants must provide the required documentation outlined in section II, part IV, items 1-7 and 9.

For clinical transplantation protocols, the Steering Committee will determine which ICR facility will produce the islets for each ICR-approved request. After distribution of the islets, the ICR Steering Committee will become informed of, and will monitor, serious adverse events involving ICR-supported protocols when the clinical investigator reports them to local and Federal oversight groups in accordance with institutional, state, and Federal guidelines. **The Steering Committee will not serve as a Data and Safety Monitoring Board for individual transplantation protocols.**

9.0 APPLICATION SCHEMA FOR APPLICATIONS UNDERGOING FULL REVIEW

Investigator submits a completed "Application for ICR Resources" to the ABCC Project Administrator following the guidelines in the application checklist

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ABCC Project Administrator distributes the Application to at least two ICR Steering Committee members* (one primary and one biostatistical) and two experts in a related field who are not members of the Steering Committee at least eight weeks before the Steering Committee meeting

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These reviewers may ask for additional information from the investigator through the ABCC Director up to four weeks before the meeting

↓

Investigator has until two weeks before the Steering Committee meeting to submit a written response to the ABCC for distribution to the designated reviewers

↓

The reviewers read the finalized application and each assign a scientific review score

↓

The primary, biostatistical and 2 non-Steering Committee member reviewers discuss the assigned application and scientific review scores at the Steering Committee meeting

↓

The Steering Committee assigns an overall review score and ranks all applications based on other considerations

↓

The Steering Committee assesses the availability of ICR resources and identifies the ICR who will provide the islets

↓

The Steering Committee makes a decision regarding the application submitted

↓

Applicant is notified by the ABCC Director of the decision and sent a copy of the reviewers' comments within approximately four weeks after the Steering Committee's decision is determined

*The reviewers may be *ad hoc* members

10.0 REQUIREMENTS PRIOR TO APPLICATION

10.1 IRB and DSMB Requirements

The clinical protocol associated with the request for islet production does not require IRB and DSMB approval at the time the application is submitted to the ICR. However, final IRB, DSMB and any relevant oversight committee approval must be documented through the ABCC before islet production can begin. In this way, the IRB and DSMB evaluation are not influenced by ICR actions. Before such approval is received, other portions of the ICR critique will be conveyed to the applicant to facilitate the protocol's modification. Islets will not be generated for a request until final approval is granted by the investigator's IRB and the relevant DSMB.

10.2 FDA Requirements

Investigators should contact the FDA, usually by telephone, to initiate conversation to identify areas of concern that may affect the success of their subsequent Investigational New Drug Application (IND) submission. The ABCC can provide FDA contact information to the investigator.

Although not required, investigators are encouraged to have initiated contact with the FDA when applying for ICR resources. Islets will not be generated for an ICR-approved request until the IND has been granted.

11.0 APPLICATION DOCUMENTS

11.1 Application for ICR Resources: Clinical Protocols

Investigators wishing to apply for ICR resources must complete an "Application for ICR Resources: Clinical Protocols," which can be downloaded at http://icr.coh.org/docs/CTapplication.doc. The following format must be used in the application to provide reviewers with the necessary information to assess the proposal. The members of the ICR Steering Committee members will review the entire application. This will include the following:

1. Checklist
2. Routing Sheet
3. Letter of Agreement to abide by the guidelines stipulated in this Policy and Procedure document, co-signed by both the principal investigator and an authorized institutional official
4. Abstract page
5. Resources (three-page limit) - address the following areas:
    a. General: Resources available to conduct the clinical trial.
    b. Clinical Trial Costs: Estimated costs and all sources of funding used to cover the expense of the clinical trial including costs to be covered by the patient or their insurer.
    c. Pancreas Procurement and Islet Processing Costs: Expected costs and all sources of funding (current and pending) for pancreas procurement, islet processing, laboratory testing, and pancreas/islet transportation. NOTE: The cost of cGMP facility maintenance and personnel employed in the isolation process will be paid for by the ICR program.

    d. ICR Support: If not previously described in a-c above, summarize those items to be supported by non-ICR resources, ICR infrastructure, or both.
    e. Use of GCRC: If an NCRR-sponsored General Clinical Research Center (GCRC) is to be used, discuss the GCRC role in the conduct and funding of the clinical trial. If other institutional, grant or contract support is being utilized, discuss the role of this support in the conduct and funding of the clinical trial.
6. Biographical Sketch of Principal Investigator and up to three additional major co- investigators.
7. Appendices
    a. Clinical Protocol. This document, including the informed consent form, must clearly state that data will be shared with the ABCC and CITR. See ICR Application for Services Appendix II for an example of standard sharing language.
    b. IRB and DSMB approval letters (may be provisional) and comments, if available.
    c. A maximum of 5 relevant journal articles published by the applicants, if available.
    d. Letters of Collaboration
    e. Approval by the appropriate institution official should be conveyed in letter format and included in the appropriate appendix.
8. Items for NIH or JDRFI Peer-Reviewed Applications:
    a. Summary Statement: Provide the statement issued to you, one for each funding agency that summarizes the critiques and findings of the panel reviewers. In some cases, this may also include a final score of the protocol. For NIH funded protocols, this can be accomplished through providing the NIH issued summary statement.
    b. Terms of the Award and Amount Funded: Provide the documentation given to you, one for each funding agency that outlines your rights and responsibilities in accepting the award, including any restrictions placed on you through the grant. Make sure to include the total amount awarded and how those funds have been allocated to you. For NIH funded protocols, this can be accomplished through providing the Notice of Grant Award (NOGA).
    c. Laboratory Information: Specify the resources available for the laboratory evaluation of trial-related clinical samples, the 1) estimated per-patient and 2) study protocol total of the number of both pancreata and ICR-produced islets required to complete the study (include the amount of islets required for testing and/or clinical use), and the tests to be provided by the ICR consortium.
9. Items for NON Peer-Reviewed Applications
    a. Proposal Summary (six-page limit). Please see ICR Application for Services Appendix I for instructions.

12.0 APPLICATION DEADLINES

"Application for ICR Resources: Clinical Transplantation Protocols" will be reviewed twice annually with decisions finalized at the Steering Committee Meetings. Applications may be submitted year-round, but submission deadlines are generally set at least eight weeks before an upcoming ICR Steering Committee (SC) meeting. ICR-SC meetings are held at least twice a year, once in the Spring and once in the Fall. For information on a specific Steering Committee meeting, please contact the ABCC Project Administrator at the below address:

Janice Sowinski
Project Administrator
Administrative and Bioinformatics Coordinating Center (ABCC)
City of Hope National Medical Center
Division of Information Sciences
1500 East Duarte Road
Duarte, CA 91010-3000
Tel: 626-256-4673 x61260
Fax: 626-930-5440
jsowinski@coh.org

13.0 REVIEW OF REQUESTS FOR ICR RESOURCES

Completed "Application for ICR Resources: Clinical Transplantation Protocols" submitted to the ABCC may undergo either an administrative review or a full review (i.e. administrative and scientific). Applications requiring full review received prior to the deadline will be reviewed by at least two ICR Steering Committee members designated as primary and biostatistical reviewers as well as two experts who are not Steering Committee members. The Steering Committee Chairperson will designate these individuals. The reviewers will receive the complete submission from the ABCC approximately eight weeks before the ICR Steering Committee meeting. The reviewers may ask for additional information through the ABCC up to four weeks before the ICR Steering Committee meeting. The investigator then has up to two weeks before the Steering Committee meeting to respond to the ABCC. The completed reviews should be submitted by the reviewers to the ABCC for subsequent transmission to the Steering Committee.

Upon receipt of each application, the ABCC will check for its technical compliance and be responsible for transmitting information to the applicants, reviewers, and Steering Committee members as needed. The ABCC will receive the written summary from each reviewer at the end of each Steering Committee meeting.

14.0 GENERATION OF ISLETS

After the Steering Committee agrees to support an application, the clinical investigator requesting islets will be asked to submit required materials to the ICR-designated facility. The investigator must work with his/her local OPO to obtain pancreata for processing by the ICR. **The investigator will be responsible for payment of OPO acquisition fees. In addition, the investigator will be responsible for the cost of 1) pancreas processing -including reagents and other isolation supplies, 2) shipping the organ to the ICR, and 3) shipping the islets to the desired location.** Costs of cGMP facility maintenance and personnel employed in the isolation process will be borne by the ICR. Final IRB approval letters and FDA Investigational New Drug (IND) number must be on file with the ABCC before any isolation will be initiated. Since multiple applications will be approved at each Steering Committee meeting, their order of implementation will be at the discretion of each ICR and be based on priority scores. The approved investigators will be apprised of the production schedule. If the ICR designated for islet generation is unable to provide adequate materials in a timely fashion, the ABCC Director will, after discussion with the requestor, delegate that responsibility to another ICR.

15.0 INTERACTION BETWEEN INVESTIGATORS, FDA AND THE ICR

It is the responsibility of the investigator to obtain FDA approval of the proposed clinical trial through an investigator-initiated IND. ICR facilities will have appropriate process and/or facilities Master Files registered at the FDA that may be cross-referenced by applicants in their IND submissions. Applicants should obtain written permission from the ICR to cross-reference the relevant master files.

16.0 DISTRIBUTION OF ISLETS TO THE INVESTIGATOR

Before islets are generated and released to an investigator for clinical use, documentation of all required final approvals must be on record at the ABCC (see Part II, Section 3.1-3.2). Once these documents are obtained, the Director of the ICR facility will assign a “protocol activation date” indicating that islets can be shipped to the investigator.

17.0 POST-DISTRIBUTION SAFETY MONITORING

17.1 Goals

Post-distribution monitoring will seek to fulfill three goals: (1) to provide quality control and quality assurance data for ICR-generated islets, (2) to provide additional information to databases generated by the ICR, NIDDK-supported Islet Registry, and other relevant organizations approved by a majority vote of the Steering Committee, and (3) to provide the ICR with the opportunity to collect and collate safety data in a centralized and systematic fashion. To attain these goals, investigators will be required to: (1) notify the ABCC of any serious adverse clinical events that occur during the course of the protocol if contaminants are detected in islets product, (2) maintain inventory records of islets, and (3) provide semi-annual clinical and laboratory updates of their protocol one month prior to each Steering

Committee meeting to permit discussion and inclusion of information into the ICR database. Satisfaction of these ICR requirements will not relieve the investigator of his/her responsibility to notify the FDA, Office for Human Research Protection (OHRP), IRB and other regulatory or oversight organizations as may be determined by local, state, or Federal requirements. These organizations must be informed at the times appropriate to their guidelines or regulations.

The Steering Committee will attempt to gather the majority of its information for post-distribution monitoring through periodic reports currently required by the FDA and funding entities. Since investigators are to submit the majority of the Steering-Committee-required documents to the FDA in a timely fashion, the Steering Committee will require that copies of these FDA reports be forwarded simultaneously to the ABCC.

The NCRR and NIDDK reserve the right to inspect the investigator's facilities and/or audit the conduct of the clinical trial. By accepting ICR resources, the investigator agrees to the above-described, post-distribution monitoring.

17.2 Documentation Required from Investigator

The following information (original or copy) must be supplied to the ABCC as a means to monitor islet use and serious adverse events. A database of such submitted documents will be maintained by the ABCC.

17.2.1 Prior to generation of islets for clinical use:

- Final Institutional Review Board approval letter
- Institutional Biosafety Committee approval letter
- The certificate of analyses for the batch of islets
- Letter from the investigators confirming FDA approval or demonstrating that the 30-day IND waiting period has passed
- IACUC approval letter for any proposed animal studies

17.2.2 After release of islets to the investigator:

- Serious adverse event reports related to the transplant protocol submitted to the IRB and/or FDA and the ICRs through the ABCC
- Protocol amendments filed with the IRB or FDA
- Annual report to IRB
- Annual report to FDA
- Data developed through studies using the ICR-generated islets
- Records documenting islet use.
- Report of islets inventory every six months
- Copies of all publications resulting from ICR support.
- Semi-annual update of patient enrollment and clinical and laboratory data

17.2.3 Notification of Study Suspension

If accrual to protocols utilizing ICR resources is suspended or terminated by the FDA or the investigator’s IRB or IBC, the investigator must notify the ABCC by telephone within 24 hours of suspension. Documentation, including suspension letters, should be forwarded to the

ABCC at the address given below within 72 hours of investigator notification.

Janice Sowinski
Project Administrator
Administrative and Bioinformatics Coordinating Center (ABCC)
City of Hope National Medical Center
Division of Information Sciences
1500 East Duarte Road
Duarte, CA 91010-3000
Tel: 626-256-4673 x61260
Fax: 626-930-5440
jsowinski@coh.org

17.2.4 Responsibility of the ICR Production Facility

Any ICR production facility or Steering Committee member that becomes aware of a serious adverse clinical event resulting from the implementation of the ICR-supported protocol or evidence of non-compliance with regulatory requirements, not previously reported to the ABCC or regulatory groups, will notify the ABCC Director immediately. The Director will then inform the members of the Steering Committee within 24 hours.

18.0 CRITERIA FOR SUSPENSION OR TERMINATION OF ICR SUPPORT

Protocols that receive ICR support will be reviewed by the Steering Committee semi-annually. Suspension or termination of use will be invoked for the following reasons:

18.1 Suspension by FDA, IRB, IBC, or OHRP

Immediate suspension of ICR support will occur if the FDA, IBC, IRB or OHRP suspends or places a clinical hold on the investigator's study. Request for reinstatement can be made only after resolution of the suspension or clinical hold. The ICR Steering Committee or Executive Committee must approve reinstatement.

18.2 Investigator non-compliance with ICR Policies and Procedures

Failure to comply with the guidelines set forth in this ICR Policies and Procedures document will serve as grounds for suspension of ICR support. Consistent failure to enroll patients or provide required clinical or laboratory data will also constitute non-compliance. The ABCC Director and the Steering Committee Chairperson will submit concerns regarding non-compliance to the investigator. Failure to reply satisfactorily within four weeks will result in suspension of ICR support. All cases of non-compliance will be discussed at the Steering Committee meeting and/or by telephone conference. ICR support for an investigator may be terminated by the majority vote of the ICR Steering Committee.

18.3 Investigator Non-compliance with Post-Distribution Monitoring

Failure to submit required documents to the ICR production facility or inadequate post-distribution monitoring will result in a letter from the ABCC requesting the

needed information. Failure to submit the required documentation within four weeks will result in suspension of ICR support until the requested documentation is received. The suspended study may not use any ICR-produced islets until the concerns are favorably resolved.

18.4 Termination of Investigator Support

Three suspensions for any of the above-mentioned reasons will result in the termination of ICR support for the current study. Investigators whose ICR support has been terminated must return any ICR-generated materials that may remain in their inventory to the ICR production facility.

19.0 QUALITY CONTROL AND QUALITY ASSURANCE

ICR facilities are required to produce islets and data in accordance with the quality control and quality assurance guidelines mandated by the Code of Federal Regulations, FDA Parts 210, 211, 312, 600, and other guidelines. ICR production facilities must disclose to the Steering Committee all quality control and quality assurance information upon the request of any member of the ICR Steering Committee. Failure to comply with FDA, NIH, or local guidelines will result in suspension of NCRR support of the ICR until the failure has been rectified and written permission has been received from NCRR.

20.0 CONFIDENTIALITY

All pre-clinical and clinical information submitted in conjunction with an “Application for ICR Resources: Clinical Transplantation Protocols” and subsequent correspondence is to be held in confidence by the ICR personnel, ABCC Staff, Steering Committee and Executive Committee.

II. ISLETS FOR BASIC SCIENCE STUDIES

1.0 ELIGIBILITY REQUIREMENTS

Applicants must be employed by and perform the proposed study within a U.S. domestic institution or government agency and also have the expertise to perform the proposed scientific study. Applications from investigators located at non-domestic institutions will be considered if the proposed research is being funded by the NIH or the JDRF. They may only be located at not-for-profit institutions. Distribution of islets to not-for-profit organizations will be subject to the restrictions of regional Organ Procurement Organizations (OPOs) that provide pancreata to the local islet distribution site.

2.0 APPLICATION AND REVIEW

All investigators requesting islets for basic research should download the "Application for ICR Services: Basic Science Islets" from http://icr.coh.org/docs/BSapplication.doc, complete the form, and submit it to the Administrative and Bioinformatics Coordinating Center (ABCC) of the ICRs by surface mail.

Applicants who wish to use the islets for a project supported by an NIH-funded or other peer reviewed grant will be subject to a brief administrative review by the Executive Committee to ensure that both IRB and IACUC regulations have been satisfied, that the scientific justification is solid and that the ICR can supply the number of islets requested for the project. These applicants will be informed of their approval status within 4-6 weeks of the receipt of their application.

Applicants who wish to use the islets for a project that has not been peer reviewed must undergo both an administrative and scientific review. Scientific reviews are conducted on a monthly basis by a subcommittee of the ICR Steering Committee consisting of two ICR and one non-ICR investigator. If the proposed project has not received peer-reviewed approval, applicants must also submit, in addition to the completed application form, a concise but thorough and informative description of the specific objectives, methods associated with the use of islets, rationale for the number of islets requested and statistical methodologies to be employed, limited to a two (2) page maximum. Recommendations will be made based on the information submitted.

All applicants will be notified of approval or reason for disapproval. If approved, applicants may then arrange for subsequent receipt of islets from all ICR centers or from specific ICRs.

The following format must be used in the application to provide reviewers with the necessary information to assess the proposal:

1. Letter of Agreement: Sign the enclosed Letter of Agreement stating your willingness to comply with Islet Cell Resource Centers (ICRs) Policy on Islet Distribution for Basic Research Studies.
2. Routing Sheet: Fill in the requested information.
3. Human Islet Request Form: Fill in the requested information. This form MUST be completed in full and returned with the application. Once islets become

available, this information will be used by the ICR laboratories to contact you and/or those you designate in your laboratory to receive islets on your behalf. If the information is not complete and accurate, you may not receive islets due to the inability of the ICRs to contact you.

4. Items for Non-Peer Reviewed Applications Applicants who wish to use islets for a project that is NOT supported by an NIH-funded or other peer reviewed grant mechanism must provide the following items:
   a) Biographical Sketch: The principal investigator and up to two (2) additional major co-investigators should each be described in a two (2) page NIH-formatted Biographical Sketch. Please use the PHS 398 form, which can be found at http://grants1.nih.gov/grants/funding/phs398/biosketch.pdf.
   b) Research Study Plan: Provide a concise but thorough and informative description of the specific objectives, methods associated with the use of islets, rationale for the number of islets requested and statistical methodologies to be employed. This plan is limited to two (2) pages.
   c) Letters of collaboration, if applicable.

Recommendations for basic science approval will be based on (1) scientific merit and feasibility of the study, (2) ICR resources required, (3) justification for the number of requested islets, (4) suitability and technical feasibility of the study (5) availability of the required laboratory support, (6) technical, legal and ethical issues of the proposed study, (7) resources required for the study, (8) current status of the study, and (9) all sources of support for the project.

3.0 APPLICATION DEADLINES

Applications are due on the first of every month. The subcommittee will review and notify applicants of approval or disapproval with sixty (60) days. Applications should be downloaded and completed and sent via surface mail to:

Janice Sowinski
Project Administrator
Administrative and Bioinformatics Coordinating Center (ABCC)
City of Hope National Medical Center
Division of Information Sciences
1500 East Duarte Road
Duarte, CA 91010-3000
Tel: 626-256-4673 x61260
Fax: 626-930-5440
jsowinski@coh.org

Upon receipt of each application, the ABCC will check for its technical compliance. The ABCC will receive the final written reviews at the end of each subcommittee meeting and be responsible for transmitting information to the applicants, reviewers, and Steering Committee members, as needed.

4.0 DISTRIBUTION OF ISLETS TO THE INVESTIGATOR

4.1 Selection of ICR and Charge Schedule

The applicant may choose which ICR(s) they prefer to supply the islets. The ICRs will ship islets using the standardized shipping protocol approved by the Steering Committee. As of February, 2008, the ICR Consortium will no longer distribute islets to for profits. Individual ICR centers can make private arrangements with commercial entities to distribute islets if they wish. Investigators from academic and government institutions beginning in January 2009 will be charged a subscription fee to access islets from the ICR Consortium. This is a change from the previous no charge policy.

By January 2009, in order to access islets on an annual basis, the subscription fee must be paid to the ABCC in full at the beginning of each calendar year. If a user is dissatisfied with an islet shipment and can document via digital photograph that the quality is poor, the Quality Assurance Administrator and the Executive Committee will review the complaint and make a determination. Under no circumstance will the subscription fee be refunded.

The subscription fee for islet access is outlined below. A semiannual charge will be implemented for January – June 2009 (subsequently, an annual fee will be imposed):

Islets Approved for Use/Year	**Total Semi-Annual Charge***
<50,000	$250
50,001 – 100,000	$500
100,001 – 200,000	$1,000
200,001 – 300,000	$1,500
300,001 – 400,000	$2,000
400,001 – 500,000	$2,500
500,001 – 600,000	$3,000
600,001 – 700,000	$3,500
700,001 – 800,000	$4,000
800,001 – 900,000	$4,500
900,001 – 1,000,000	$5,000
>1,000,000	TBD. Annual orders in excess of 1 million islets must receive pre-approval by the ICR Consortium Executive Committee

The ICR will also provide flash frozen islets. Excess islets that cannot be distributed can be flash frozen by the ICR centers and stored in vials of 10,000 islets. At regular intervals, the ABCC will announce to all approved users, the availability of these islets. These islets will be counted against the yearly quota assigned to each users. The ICR centers will be reimbursed for these islets at a reduced rate.

Those monies will be considered as program income for the ICR grant and must be accounted for in the ICR Annual Report to the National Center for Research Resources (NCRR).

4.2 ICR Reimbursements for Pancreas Acquisitions:

The ABCC is responsible for tracking all pancreas acquisition invoices submitted by the ICRs and for initiating payment based on reimbursement funds available from NIH. These reimbursements will be made according to established NIH policy.

4.3 ICR Reimbursements for Islet Cell Distributions:

The ABCC is responsible for tracking islet distributions from each ICR center on a quarterly basis. The ABCC will submit an invoice request to each center with a listing of the source of funding NIH or JDRF per quarter. Each center will then invoice the ABCC for the distribution and the ABCC will remit the required payment to the ICR center, not to exceed $62,500 per quarter per center, based on a reimbursement rate of $0.10 per islet shipped.

4.4 Material Transfer Agreements (MTAs)

In addition to completing the basic science application, investigators may be required to complete an MTA from the ICR supplying the islets and/or the Organ Procurement Organization (OPO) who supplied the pancreas to the ICR. All institution specific requirements will be furnished by the ICR supplying the islets and must be completed before the investigator receives islets.

4.5 Shipment Specifications

Prior to islet shipment, the recipient must complete the “Human Islet Request Form”; an example of this form is provided in the application. This form outlines shipment information such as recipient’s address, express shipping account number, desired tissue specifications and other relevant information. The recipient is expected to pay shipping costs. The ICR will send shipments to the user in standardized ICR packaging. The user is required to return this packaging to the ICR center that provided the islets. The ICR center will pay for this return shipment. The user will be ineligible to receive another shipment until the user has returned the packaging to the ICR center.

4.6 Islet Characterization at ICR

Limited donor information, isolation data, islet specifications and release criteria will be provided by the ICRs using the “Tissue Shipment Form”; an example of this form is provided in the application. This form will accompany or closely follow the islet shipment.

4.7 Islet Assessment

The recipient can access online a “User Feedback Form” on which they can convey their level of satisfaction with the quality and quantity of the islets they receive”; an example of this form is provided in the application. This form must be completed on line and submitted to the ABCC before the user is eligible to receive another islet

shipment. The ABCC will track user satisfaction and provide annual summaries to the NCRR and ICRs.

Filing a Complaint Regarding Islet Quality:

Should a user be dissatisfied with the poor quality of an islet shipment under the new subscription fee process, the user may file a complaint with the ABCC and must document the poor quality preparation with a digital photo. This photo will be reviewed by the Quality Assurance Administrator and the Executive Committee and a determination made. If the complaint is deemed justified the shipment will not be deducted from the users yearly islet limit. The ABCC will notify the user of the outcome of this review.

5.0 TERMS OF ACCEPTANCE

Investigators agree that:

1. Human islets obtained through the ICRs will be used for approved basic research purposes only. Human islets provided through this program may not be used for human transplantation. Studies that address clinical transplantation should be submitted as a Clinical Application to the ICR Consortium.
2. The "User Feedback Form", found in the application, will be completed online and returned to both the ABCC after each shipment of islets received. Failure to submit this information will disqualify the investigator from receiving any basic science islets until the form is completed and returned.
3. Human islets and/or islet products obtained through the ICR Basic Science Islet Distribution Program will not be transferred to a third party unless authorized through Executive Committee review. All collaborators and their affiliations must be identified on the application.
4. Users will disclose all forms of support for the project, private or academic collaborations, and fiduciary relationships relevant to the project for which the islets are being provided.
5. Approved users will pay shipping costs from the islet distribution site to his/her laboratory.
6. Approved users will return all packaging to the ICR distribution site from whom the islets were received. Failure to do so will deem the user ineligible to receive islets until the packaging has been returned. The ICR center will pay for the return shipment.
7. Approved users will abide by the ICR Policy and Procedures document found at http://icr.coh.org/docs/icrpp.pdf.
8. Approved users will cite the "ICR Basic Science Islet Distribution Program" and/or the appropriate islet distribution site in any publications, press releases or abstracts resulting from the use of the human islets. A reprint of the document where the acknowledgement is made must be submitted to the ABCC.
9. Users agree to pay an annual subscription fee due at the beginning of each calendar year before they may access ICR islets. For 2009, this subscription fee will represent a semi-annual fee and will encompass the period from January through June 2009.

An approved investigator request will remain active during the life of the grant project under which the request was submitted and as long as the above conditions are met. The ABCC will provide the user with a yearly approved limit based on the total project limit. Competing renewals of the grant project or new projects will require a re-application to the ABCC. If additional islets above the approved project limit are needed and the grant is still active, the user may, once a year, request an increase in his/her islet limit using the ICR Human Islet Increase or Extension Request Form (see attachment). Each user request will require a scientific justification for the increased need for islets and will be reviewed by the Executive Committee. The ABCC will inform the user of the outcome of this review. If the Executive Committee approves the islet increase, the user will be responsible for the additional subscription fee to cover the cost of receiving additional islets.

6.0 TERMINATION OF AGREEMENT

Failure to comply with the conditions stated above will result in cancellation of this agreement.

7.0 CONFIDENTIALITY

All pre-clinical and clinical information submitted in conjunction with an “Application for ICR Resources: Basic Science Islets” and subsequent correspondence will be held in confidence by the ICR personnel, ABCC Staff, Steering Committee and Executive Committee.

Attachment

ICR Human Islet Increase or Extension Request Form

Investigator:

Institution:

Name of grant supporting human islet usage:

Grant number:

Start date of grant:

End date of grant:

Source of grant funding:

Number of islets required per year:

Number of islets required to complete project:

What rate of islet usage do you currently have?

What specific increase in islet shipments is requested?

Provide some justification based on the existing research that the increase requested will meaningfully alter/transform/facilitate the ongoing research. The increase should fill some current unmet void that PI's should detail in more than a sentence.

Your publications citing the ICR as the source of islets:

Number of publications:

Titles:

The following should include the reason why an increase is needed. A stated objective or list of objectives, a description of the studies user intends to perform, a brief methods section, the total number of islets user will need to support the study and information with regard to the size and frequency of each shipment:

Scientific Justification to Request Extension or Islet Increase of Current ICR Approved Project: