



Policies and Procedures for the Integrated Islet Distribution Program's (IIDP) Islet Isolation Centers (IICs)

Contact Information:

*James Cravens, M.P.H, Program Manager
Integrated Islet Distribution Program
City of Hope
1500 East Duarte Road
Duarte, CA 91010-3000
phone: 805-201-1963
e-mail: jcravens@coh.org
website: <https://iidp.coh.org/>*

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1.0 IIDP MISSION STATEMENT

1.1 The goal of the Integrated Islet Distribution Program (IIDP), funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), is to work with the leading human Islet Isolation Centers (IICs) to distribute high quality human islets and associated tissues and data to the diabetes research community, to advance scientific discoveries and translational medicine.

1.1.1 As subcontractors for the IIDP, the fundamentals of this IIDP Mission Statement should also serve as guiding principles for all IIDP IICs, as well.

1.2 IIDP Human Islet Isolation Centers (IICs)

The IIDP Coordinating Center (CC) subcontracts with a group of academic, and/or private laboratories as our core IICs. All centers are bound by the language of the subcontract, its appendices, and policies.

1.2.1 The following IIDP isolation centers provide human islets, non-islet pancreatic tissue (acinar), ancillary tissue, and data for distribution through this program:

- Loyola University Medical Center: *Director, Dr. Luis Fernandez*
- The Scharp-Lacy Research Institute: *Director, Dr. David Scharp*
- Southern California Islet Cell Resource Center: *Director, Dr. Fouad Kandeel*
- University of Miami: *Director, Dr. Camillo Ricordi*
- University of Pennsylvania: *Director, Dr. Ali Najj*

2.0 PURPOSE

The purpose of these policies and procedures is to provide required guidelines regarding the execution of this project and compliance with the guidelines set forth. The IIC will furnish all the necessary services, qualified personnel, material, equipment, and facilities, as needed to perform the work set forth below, unless otherwise stated. It is the intent of the IIDP Principal Investigators (PIs) and IIDP staff to work closely with the IICs to ensure satisfactory completion of work and to do so in a collaborative and collegial manner.

3.0 IIC PROCEDURES

3.1 Implementation of Standard Operating Procedures (SOPs)

The IIC will be required to implement the Standard Operating Procedures (SOPs), which can be found at <https://iidp.coh.org/centers/Policies-Standard-Operating-Procedures>, and [Protocols.io](https://iidp.coh.org/protocols) for 1) [culturing](#) and [shipping islet equivalents](#) (IEQ) and other related tissues, 2) data entry, and 3) quality assurance testing as provided by the IIDP and other SOPs as developed and deemed necessary by the Project Scientist, Program Official, External Scientific Panel (ESP), IIDP PIs and Program Staff over the course of this Agreement. SOPs will be located on the web at iidp.coh.org and may be changed from time to time at the discretion of IIDP. The IIC will be notified through email by IIDP when such a change occurs.

3.2 The Use of IIDP Algorithm for Islet Distribution

The IIC agrees to use the IEQ distribution algorithm provided by the IIDP for the purpose of fairly and equitably distributing the IEQ produced under the Program. IICs will be instructed on the proper use of the algorithm and the order by which the IEQ must be distributed to the IIDP recipients. This will ensure the best match to donor and islet parameters as requested by the IIDP researchers as well as considering the requested waiting time between islet shipments.

3.3 Production and Distribution of Human Islets, Non-Islet Pancreatic Tissue (Acinar), Flash Frozen Islets, and Histology Sections of the Native Pancreas

3.3.1 IIC Islet Production Levels

Each year the IIC agrees to produce up to, but not exceeding, the islet total specified in its IIDP subcontract (“the cap”). Should the demand for IEQ fall, the IIC may be asked to produce fewer than this estimated cap, or conversely should the demand increase, the IIC may be asked if they have the capability to produce additional IEQ above the cap.

3.3.1.1 The IIC agrees to work closely and cooperatively with the IIDP to optimize the production of IEQ shipped through the IIDP program. Should production levels fall below expectations for any quarter, the IIC will be required to increase IEQ production in the subsequent quarter to a level determined collaboratively by the IIDP PIs and Subrecipient (Isolation Center Director) to maintain a sufficient supply of IEQ for the program. Should the contracted IIC fail to maintain production minimums for two (2) consecutive quarters, the IIDP, at its sole discretion, may terminate the subaward per contract.

3.3.2 IEQ Shipments

Overnight shipping of IEQ between multiple sites, domestic, or international, must be shipped in accordance with Standard Industry Practice; FDA requirements approved SOPs, city, state, and/or Federal regulations, and any special instructions given.

3.3.2.1 Minimum Shipments: The IIC may fill orders of fewer than 1000 IEQ at their discretion but for orders of >1000 IEQ, it is the responsibility of the IIC to fulfill all requests in the order that they are populated on the website under Broadcast Confirmation.

3.3.3 Flash Frozen Islets

On those occasions when not all IEQ can be placed from an isolation, the IIC may flash freeze the unplaced IEQ, if the IEQ are > 80% pure, according to the SOP for flash freezing islets found on the IIDP website. The IIC is required to post the number of available flash frozen islets on the IIDP site, and is required to hold these IEQ at -40°C to -70°C in their laboratory until an IIDP investigator submits a formal request to receive the flash frozen IEQ.

3.3.3.1 The IIDP will reimburse the IIC at the next payment cycle following posting, at the standard reimbursement rate for human islets (see 3.5 Table 1). At the time of acceptance by an IIDP researcher, the IIC will ship the interested researcher the requested islets per SOP, through Priority Federal Express overnight shipping, on dry ice, at the recipient’s expense. IICs are encouraged to flash freeze between 1-5 vials of IEQ at 1,000 IEQ for each isolation for which all IEQ were not placed through the distribution system. The IIC may only freeze up to a maximum of 50,000 reimbursable

IEQ per subaward year (50 vials x 1,000 IEQ/vial, where possible). The flash frozen islets will be counted towards the IIC's annual cap.

3.3.4 Provision of Non-Islet Pancreatic Tissue (NIPT) / Acinar

The IIC will provide NIPT / acinar tissue in the amount and condition (fresh or frozen) requested by the investigator when possible with each isolation. Requests can be made as fresh, which is offered and shipped on the day of the islet/acinar isolation, or flash frozen, which can be stored at -40°C to -70°C in their laboratory until a mutual agreeable time for shipment on dry ice at the researcher's expense. The IIC will be compensated as defined below for acinar distribution in **3.7** Table 1.

3.3.4.1 From each islet isolation distributed via the IIDP, the IIC will provided 2mL of flash frozen NIPT/acinar tissue to the IIDP's Human Islet Genotyping Initiative (HIGI) lab located at Stanford University. Each of these samples will be frozen and shipped in a batch to HIGI at the beginning of each calendar quarter. (see Table 1 for compensation.)

3.3.5 Provision of Histology Sections form the Native Pancreas

A sample from each pancreas should be taken after the pancreas has been trimmed of extraneous tissue and prior to the perfusion with enzyme. A 1cm x 1cm biopsy should be removed from the neck of the pancreas, near the section where the pancreatic duct is cannulated for collagenase infusion. The sample should be fixed in formalin for 24±8 hours, rinsed with Phosphate Buffered Solution, held in 70% ethanol, and sent to the IIC's pathology core for embedding. The samples, embedded in a paraffin block, should be mailed to the COH's Pathology Cores & Biobanking| Shared Resources monthly (see **3.5** Table 1 for compensation). Sectioning, staining, analysis, and image posting will be orchestrated by the IIDP CC for every isolation.

3.4 IIDP Islet Quality Standards

The IIC agrees to produce IEQ in accordance with the standards set for quantity and quality and agrees to provide the required test results confirming these standards for IEQ shipped. These tests shall include IEQ: 1) quantification, 2) grade 3) purity, 4) viability, 5) sterility and 6) functionality. Additional tests may be performed at the discretion of the IIC and submitted through the IIDP website to provide additional information to the IIDP recipients about the quality of the islets. To ensure consistent product quality, the IIDP has set the minimum requirements to be accomplished by IICs on all islet preparations provided to the IIDP for distribution.

The results of the following IEQ quality assurance assessments will be made available by the IIC at the time of the islet offering (broadcast) by entering into the IIDP database:

3.4.1 Quantification and Grade

Dithizone-staining, followed by assessment of islet number, size, and quality ranking using light microscopy with visual examination by 2 qualified personnel (or double counting by one individual of a duplicate sample) should be performed and reported within 6 hours of shipping. Most studies show that the maximum loss of islets occur in the first 12-18 hours post isolation. Per IIDP islet shipping protocol, it is recommended that islets be cultured for at least 48 hours and required to be cultured a minimum of 18 hours at 37°C post isolation, prior to shipping. Our own publication from a comparative study, [*The Optimal Time to Ship Human Islets Post Tissue Culture to Maximize Islet Recovery*](#), shows the best culture time may be even longer.

3.4.2 Digital Uploading of Count Sample Image

The dithizone-stained islet count sample should be placed in a 60mm culture dish that is etched with a 2mm grid on the bottom dish. Two magnifications of the image should be uploaded to the broadcast system: a low magnification where the majority of islets (>30) centered in the dish are seen in the image; a higher magnification where a portion of the islets (10-20) can be seen in the image, This would be similar to the magnification used for counting the islets. Uploading should be performed each time an islet count is required.

3.4.3 Purity

Dithizone-staining and determination of the islet-to-acinar ratio by volume using visual examination under microscope by 2 qualified personnel (or double counting by one individual of a duplicate sample) should be performed and reported after culture and prior to shipping. Human islet preparations will contain $\geq 80\%$ for “most pure” and $\geq 50\%$ (minimum for reimbursement) for “impure” islet tissue as determined by dithizone staining and light microscopy.

3.4.4 Viability

Fluorescent dye method using fluorescein diacetate and propidium iodide or other similar dyes selected by the IIC that determine cell viability with visual examination by 2 qualified personnel (or double counting by one individual of a duplicate sample) should be performed and reported after culture and within 6 hours of shipping. Dyes can be substituted for other inclusion and exclusion dyes with the permission of the IIDP. Human islet preparations will consist of $\geq 80\%$ viable islet particles as determined by fluorescence microscopy. Reimbursement for islet preparations will be done for preparations which are documented as $\geq 80\%$ viable.

3.5 Preliminary Assessment Results

The preliminary results of the following IEQ quality assurance assessments should be provided within 10 days of broadcast and final results provided within 30 days of broadcast via entry into the IIDP database:

3.5.1 Sterility

Testing for microbial (both aerobic and anaerobic) and fungal contamination must be performed on the final preparation. Preliminary results must be reported to the IIDP within 10 days of shipping. Final results must be reported within 30 days of shipping.

3.5.2 Sterility Monitoring through Sentinel Flasks

In addition, a sentinel flask of ≥ 100 IEQ should be aliquoted at the time of shipping and kept in house for approximately 1 day in PIM-T at 6° C followed by 2 days at 37° C in PIM-R, in order to monitor islet quality in the event of complaints by the receiving investigators concerning contamination or islet quality.

3.5.3 Functionality Assay

Glucose Stimulated Insulin Release (GSIR) assay should be performed, according to the IIDP SOP, using triplicate samples of islets after 37° C in culture medium for at least 12 hours. Final results of the assay must be reported to the IIDP within 10 days of shipping.

3.6 Quality Standards Revisions

Quality standards will be defined by the current SOPs found on the IIDP website and Protocols.io. Quality standards may change over time as better methods are developed and accepted scientifically as the preferred technique. Any changes to quality standards will be discussed with the IICs, but decisions made to change such standards will be at the sole discretion of IIDP. When new SOPs are initiated, the IIC will be notified through email, and the SOP will be placed on the IIDP website and/or Protocols.io.

3.7 Compensation to IICs for Distribution

As an NIH-sponsored project, the IIDP requires that each IIC work within the budget provided by NIH. However, evaluation is regularly conducted to determine if future changes to the IIDP reimbursement structure are warranted. The IIDP currently reimburses its islet production centers according to the following rate structure:

Table 1. IIC Compensation Schedule as of December 1, 2021:			
Human Islets			
	Non-Profit Recipients	Non-diabetic donors	\$0.12 per IEQ
		T2D donors	\$0.20 per IEQ
	For-Profit Recipients	Non-diabetic donors	\$0.19 per IEQ
		T2D donors	\$0.24 per IEQ
Flash Frozen Islets		1,000-IEQ vial	\$120 per vial
Pancreas Sample for Histology			\$250 per islet isolation
Non-Islet Pancreatic Tissue (Acinar)		Researchers and HIGI	\$200 per sample

3.8 Reimbursements Based on Quality Standards

The IIC agrees not to ship any IEQ that do not meet the quality standards set for the program for purity, viability, and contamination. If IEQ of lesser quality are inadvertently shipped, the IIC will not be reimbursed for these IEQ. If after testing, IEQ should prove to be contaminated and/or not meeting the listed viability, the IIC will be considered for reimbursement for the IEQ of the first such instance contingent upon available IIDP resources, but any and all subsequent islet isolations during the performance period proven to be contaminated and/or less viable will not be reimbursed. Reimbursement will be made to the IIC for all useable IEQ produced that meet the requirements set forth by IIDP as provided in the IIC contract

3.9 Invoicing

The IIC will submit bimonthly (6 times per year) invoices for payment within fifteen days (15) days of the end of each reporting month. Invoice must include the name and address of the IIC, total payment requested, taxpayer identification number, number of IEQ, Subaward Number, and the description of payment requested.

3.10 IIC Data Collection

The IIC agrees to provide all required data to properly engage the IIDP algorithm for the fair and equitable distribution of human islets to IIDP investigators and to provide the program with accurate information needed to describe the quality of the islets and tissues being distributed as listed in 3.3 above.

3.10.1 The IIC agrees to supply all IEQ processing and donor information data points that are required by the IIDP's web-based Islet Allocation System (IAS) at the time of broadcast for the purposes of broadcasting IEQ including all low resolution HLA typing, donor diabetic information, Hemoglobin A1C data, isolation information, and required Quality Standards, as listed above.

3.10.2 All shipping confirmation data used to verify or cancel shipments must be completed within 4 hours of the IIC's stated shipping deadline in order to provide accurate and timely shipment status information to the IEQ recipient.

3.10.3 If the IIC does not abide by these conditions, compensation may be withdrawn.

3.11 Media and Shipping Supplies Stewardship

The IIC agrees to be good stewards of the materials provided to them by the IIDP towards the exclusive use of this distribution program. These materials include supplies of media for the culture and shipment of human islets and other required tissues, and necessary shipping materials to provide safe and temperature appropriate means of shipment of said tissues.

3.11.2 The IIDP provides to the IICs all media and its additives (Ciprofloxacin and Human AB Heat-inactivated Serum) used for islet culture and shipment as well as all shipping supplies needed for transport of islets and other supplemental tissues to all IIDP researchers and other subcontracted centers (at an average of \$805 per isolation).

3.11.3 Other subcontracted centers currently include:

1. Human Islet Phenotyping Program (HIPP) at Vanderbilt University
2. Human Islet Genotyping Initiative (HIGI) at Stanford University
3. Pathology Cores & Biobanking| Shared Resources at City of Hope
4. Other contracted IICs as needed

3.11.3.1 IIDP provides, to the IICs, shipping account numbers for all shipments made to any of the subcontracted centers.

3.11.3.2 IIDP provides to the IICs shipping account numbers for each IIDP researcher to be used for the shipment of tissues to the said researcher.



3.12 IIC Performance Reviews

There will be an annual performance evaluation of the IIC conducted by the IIDP staff and reviewed by the IIDP Executive Committee. Should there be documented performance issues, the IIDP staff will work with the IIC to identify any issues and assist to try to rectify them. If the problem areas cannot be satisfactorily corrected, the IIDP shall have the right take remedial action as may be necessary, up to and including the decision not to renew the IIC subcontract. Performance metrics that will be evaluated include: 1) satisfactory IEQ production, quality and viability 2) compliance with IIDP SOPs; 3) distribution of IEQ via the IIDP IAS; 4) distribution of non-islet tissue as requested; 5) stewardship of the supplies provided by the IIDP to the IICs exclusively for the distribution program; or 6) compliance with new processes and procedures which the IIDP may reasonably implement with adequate reimbursement, with the advice of the External Advisory Board and Executive Committee.