**Financial Issues Constraining the Use of Pancreata Recovered for Islet Transplantation: A White Paper**

**Background:**

Cellular transplantation is a rapidly growing new field of transplantation that has the potential to impact a diverse spectrum of human disease. The most prominent example of the promise of this form of therapy is the recent impressive success of isolated islet transplantation in select patients with severe metabolic complications of type I diabetes (1, 2). Although islet transplantation is not yet considered an established therapy, it is currently under intense clinical investigation supported by National Institutes of Health (NIH) and the Centers for Medicare and Medicaid Services (CMS) in the form of two new registration trials. Thus, the procedure is poised at a critical juncture in its development. Its validity as a safe and efficacious therapy for select patients with type 1 diabetes will be judged in the next 3-4 years based on forthcoming results of these trials. A major impediment to pancreas organ utilization and thus to further progress in the field is the cost of the deceased donor derived organs that are processed to generate isolated islet preparations used for trials in islet transplantation.

In 2004, ten societies broadly representing the field of transplantation commented in a Joint Society Letter to CMS to express shared concerns regarding proposed methodology for payment for pancreatic islet transplantation. Important progress was made based on those communications. However, because of recent changes in the field during the intervening three years, and the recent ruling by CMS regarding "intent to transplant" (CMS-1543-R Dec. 21, 2006: Allocation of Donor Acquisition Costs Incurred by Organ Procurement Organizations (OPO's)), we contend that the current methodologies prescribed by CMS for categorizing the costs and developing the Standard Acquisition Charge (SAC) for pancreas used for islet transplantation are incongruent with the clinical innovations. Thus, it is essential to reexamine the current cost accounting practices to identify and resolve conflicts between the missions of the key stakeholders in islet transplantation, such as CMS, NIH, HRSA, Food and Drug Administration (FDA), the Association for Organ Procurement Organizations (AOPO), the United Network for Organ Sharing (UNOS), the Juvenile Diabetes Research Foundation (JDRF), and the scientific transplant community.

It is estimated that currently the organ acquisition related costs for rendering a single diabetic patient insulin independent by islet transplantation, which generally requires transplantation of cells procured from pancreata from 2-3 deceased donors, is between $50-90,000 (3). This cost is dramatically increased, up to 2 fold (or $180,000 per patient), by including the cost of pancreata that are isolated with the consideration of transplant but from which the preparation proves unsuitable for transplant (i.e. preparations that do not meet standardized and generally accepted product release criteria for transplantation). Because the procedure is currently being supported at the 20-30 active islet centers in the US only by grant and institutional funds, the thorough exploration of isolated islet transplantation as a viable biologic therapy is being

jeopardized by the cost of cadaveric organs. In fact, the rate of islet transplantation has decreased and many islet centers have already reduced or discontinued islet production because of these costs. According to the Collaborative Islet Transplant Registry (CITR), the number of new islet transplant recipients peaked in 2002 but the subsequent three years averaged one third fewer transplants (4). In addition, UNOS membership data indicates that of 47 transplant centers with registered islet transplant programs, 19 elected not to apply for UNOS membership in 2005.

Only a few centers in the US are funded by the NIH for clinical islet transplantation. The NIH funded Clinical Islet Transplantation Consortium(CIT) is in the midst of initiating a series of phase II and phase III clinical protocols in the US in islet alone patients and islet after kidney patients (5). It is expected that this group of studies will include enrollment of approximately 100 patients over the next 3 years. Islet transplantation investigations outside the CIT will be exceptionally difficult to conduct due to the prohibitive cost of the needed organs. This will markedly impair assessment and application of novel strategies designed to improve the success and safety of the procedure.

The cost of pancreata for islet transplantation is a potent negative stimulus for pancreas organ utilization in the US. This is contrary to the goals of HRSA, and UNOS which wish to maximize deceased donor organ recovery and utilization. The recent Health and Human Services (HHS) Breakthrough Collaborative that seeks to maximize organ utilization holds as critical metric for success increasing the number of organs per donor. Enhancing pancreas utilization is essential to achieving this goal. In addition, pancreata allocated for transplant and research are now a specific performance measure for OPOs. Moreover, the efforts of the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) and the National Institute of Allergy and Infectious Disease (NIAID) which have been charged to conduct trials in islet transplantation may be compromised by the cost of the required organs. Finally, this problem can be seen to conflict in principle with the intentions of Congress which appropriated funds specifically to study Type I diabetes, and by way of the Medicare Modernization Act (MMA), Section 733(a) of Public Law 108-173, directed NIDDK to perform research in islet transplantation research as a therapy for Type I diabetes.

**The problem:**

We have identified two specific problems related to organ costs for islets, that if rectified could result in significant increases in utilization of cadaveric pancreata and promote further scientific evaluation of islets as a biological cellular therapy for Type I diabetes: 1) current regulations do not adequately delineate the criteria by which donor pancreata recovered for islet transplantation can be considered unsuitable for transplantation and therefore billed at a discounted rate, and 2) that application of full standard acquisition charge (SAC) for pancreata which result in islets that are successfully transplanted may be unjustified. We believe it is important to consider these issues separately.

1) Unlike most forms of whole organ transplantation in which a decision regarding intent to transplant can be made at the time of organ recovery, the point of deciding intent for islet transplantation occurs much later in the process. Pancreata processed with the possibility of transplantation have a high rate of not yielding a clinically suitable preparation as defined by standardized and widely accepted transplant release criteria. In most major series studying islet transplantation, this rate is approximately 50% (1). Thus a decision regarding intent occurs only after the organ has been fully processed and in most cases, after completion of a period of in vitro culture. These facts highlight the inherent differences between cellular islet transplantation and whole organ pancreas transplantation.

When islet preparations are found to be unsuitable for transplantation, there is currently variability among OPO's across the country as to the appropriate charge applied to such organs. The Medicare Intermediary and some OPO's hold the position that a full SAC is required based on the CMS Final Rule (CMS-1428-F), and others interpret the regulations as to allow there to be a lesser research charge for such unsuitable organs when the resulting islets are deemed non-transplantable. We believe that the confusion in how these organs are classified is attributable to ambiguity in the language in the preamble to the Final Rule implementing the islet transplant provisions of Section 733(a) of Public Law 108-173 of the Medicare Modernization Act, which includes the following Comment and CMS response published August 11, 2004 (effective October 1, 2004: FY 2005 IPPS Final Rule, 69 48953):

> "Comment: Some commenters asked for guidance on the appropriate methodology for OPOs to use in identifying costs incurred in procuring pancreata for islet cell transplantation. Some OPOs have indicated that they currently are providing pancreata for islet cell transplantation but do not receive their full standard acquisition charge (SAC) for the organ.
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> Response: In some cases, OPOs have been billing pancreata for islet cell transplant at a lower tissue rate. This is an improper billing method. The quality and resources required to procure the organ are identical, and a full charge should be made. **Organs that are determined to be nonviable can be billed at a lesser research rate."**
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> However, the language used by CMS above, (specifically the term "non-viable") does not adequately differentiate "non-viable" whole organ pancreata from "unsuitable" islet preparations. Whereas whole organ pancreata may be readily judged non transplantable at the time of organ procurement, this is not possible for pancreata recovered for islets. In the case of islets, a decision regarding suitability and therefore intent to transplant can not be made until completion of the manufacturing process, including the isolation, purification and assessment steps needed to generate a final product. To encourage attempts at islet transplantation by the islet transplant community, we believe that it is essential

that CMS provide clarification of the CMS Final Rule on this topic (see "Proposed Actions Items").

Clarity on this issue will help to ensure that the OPOs recoup the nominal additional direct costs incurred for the pancreas recovery without unduly burdening the islet transplant centers when the resulting islet preparation is either unsuited for any use or is relegated to islet related research. Not providing a defined charge structure for this common occurrence could introduce disincentives for the OPOs to promote pancreatic islet transplantation.

2) With respect to the current charge for pancreata that do yield transplantable isolated islet preparations, we believe there are sound arguments to support their recovery at a charge different from the SAC applied to pancreata recovered for transplantation as whole organs. Islet and whole organ transplantation differ in a number of critical respects in addition to the point at which intent to transplant is determined. First, unlike whole organ transplantation, gaining insulin independence by islet transplantation generally requires processing of multiple organs to recover an adequate islet mass. This leads to marked increases in the overall cost which is particularly problematic since this therapy is not yet FDA approved and reimbursable. In many respects, this is an issue of potency that is similar to that encountered in 2-for-1 renal transplantation in which a single organ charge is levied because of the lesser effect or potency of the organs being utilized.

Second, islets are regarded by the FDA as cellular/tissue transplants and unlike whole organ transplantation are therefore subject to good tissue practice (GTP) regulations (6). Based on this classification, it is reasonable to distinguish islets from whole organs with regard to SAC and subject them to both a cost accounting treatment and a resulting charge more in line with that for the recovery of other tissues. The surgical approach used to recover a pancreas for islets may differ from whole organ recovery in some circumstances, such as when there is no possibility that the pancreas will be transplanted as a whole organ. While these differences provide an important precedent for regarding islet transplantation as distinct from whole organ transplantation, it must be also recognized that unlike other tissues that are recovered such as heart valves, islets are metabolically active cells in which proper physiological function is essential to success post transplant. Based on these facts, we suggest that a unique designation as a "metabolically active tissue" is needed for whole organs recovered for cellular/tissue therapy, such as in the case of pancreata recovered for islets.

CMS treats pancreases for islet cell transplantation the same as for whole pancreas transplants despite islet transplantation not yet being considered an established therapy. The policy results in pancreases for islets using full organ costing, and OPOs are thereby forced to price organs to bear these costs. As noted earlier, the recent intent ruling has exacerbated the challenge to programs as they seek to recover as many organs as possible knowing that the number found to be unusable or non-viable may be significant.

Finally, we recognize that the federal Medicare program is concerned with cost-shifting of expenses from non-renal categories. We do not believe that the proposed revisions to costing and the subsequent charging for pancreata recovered for islets would inappropriately shift costs. We believe these approaches would allow more accurate and ultimately more beneficial methodologies. While CMS may initially perceive that these changes carry implications with respect to total Medicare payments for organ acquisition, it is important to recognize also that the additional pancreata utilized for islets are organs that might otherwise go to waste. Ultimately, increased volumes of both organs and metabolically active tissue recovered would allow a reduction of indirect expense per specimen whether it is a kidney or another organ or tissue.

**Proposed Action Items:**

Based on our objective to facilitate successful pancreas allocation, and the goal to promote development of islet transplantation as a novel therapy for patients with Type I diabetes we suggest the following:

1) Clarify the language in the CMS Final Rule so that it is understood that pancreata are determined to be unusable for islet transplantation by taking into account the suitability for transplantation of the final islet product following the islet manufacturing process. Specifically, we suggest addition of language to the final rule stating that: **"Intent to transplant decisions regarding pancreata allocated for islet transplantation are made after the isolation has been completed and full cellular product release testing performed. Pancreata allocated for islet transplantation that do not yield a final islet preparation suitable for clinical transplant can be treated for cost accounting purposes as tissue, so as to allow for a lesser charge for the pancreas. The islet cell processor must provide suitable documentation to the OPO referencing the laboratory results."** We consider it equally important in this regard that CMS provide specific clarification and direction to the Medicare Intermediary concerning this issue. In addition, we seek clarification that pancreata initially allocated for transplantation that do not meet release criteria and are used for research purposes, can be counted as research organs with respect to OPO performance measures.

2) Incorporate development of a new designation of islets as a "metabolically active tissue/cellular transplant" to account for its unique properties that differentiate it from both whole organ and tissue transplantation. Thus, the cost accounting methodology as applied to transplantable tissue should also apply to pancreata processed and transplanted as islets. This action is justified based on critical differences in whole organ and islet transplantation including the need for processing multiple organs for a single recipient, and recognition of the significant technical differences in the nature of the recovery process for pancreata recovered for islets versus whole organ transplantation.

In summary, the objectives to maximize organ utilization, to accurately and properly determine the costs and to properly distribute organ acquisition charges, and to develop and promote cell based therapies such as islet transplantation are goals shared by each of the groups working in the field of transplantation. The conflicts inherent in the current rules do not allow the OPO costing and charging methods to correspond. The rules also have set up a financial conflict between organizations at each stage of islet cell use that cannot currently be overcome without a reexamination of the financial rules. We recognize further that the above recommendations represent just one means to help achieve these goals and that other equally acceptable approaches may exist. In addition, we recognize that the therapy remains in dynamic evolution and that it is hoped and expected that future technical advances will overcome the problems of islet isolations that fail to meet release criteria, and the need for multiple successful isolations per recipient. We thus anticipate that future modifications may be required as the discipline of organ derived cellular therapies matures.

**American Society of Transplant Surgeons**
**American Society of Transplantation**
**Association of Organ Procurement Organizations**
**American Society of Multicultural Health and Transplant Professionals**
**Cell Transplant Society**
**Diabetes Research Institute Foundation**
**International Pancreas and Islet Transplant Association**
**Juvenile Diabetes Research Foundation**
**Principal Investigators of the Clinical Islet Transplantation Consortium**
**Principal Investigators of the Islet Cell Resource Centers**
**The Organization for Transplant Professionals (NATCO)**
**The Transplantation Society**

## References


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