National Institute of Diabetes and Digestive and Kidney Diseases
Diabetes Mellitus Interagency Coordinating Committee
Meeting on Islet Transplantation

Democracy 2, Room 701
6707 Democracy Boulevard
Bethesda, Maryland

November 23, 2004
Summary Minutes

WELCOME AND INTRODUCTIONS

Judith Fradkin, Director of the Division of Diabetes, Endocrinology, and Metabolic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), welcomed the Committee members and guests. She stressed the importance of this meeting on islet transplantation because of recent legislation that will impact National Institutes of Health (NIH) initiatives and programs. The Pancreatic Islet Cell Transplantation Act of 2004 was passed by the U.S. Congress in November and included two key provisions; one making pancreata procured by an organ procurement organization (OPO) and used for islet cell transplantation count for purposes of certification by the Center for Medicare and Medicaid Services (CMS), and the second giving new responsibilities to the Diabetes Mellitus Interagency Coordinating Committee (DMICC) regarding islet transplantation. The DMICC is mandated to report annually on progress in implementing the Act. One purpose of this meeting is to begin discussing approaches being initiated by DMICC member agencies, either independently or through cooperative arrangements with other agencies, that can be included in the mandated report.

Dr. Fradkin reviewed additional legislation related to islet transplantation, including section 733 of the Medicare Modernization Act (MMA), which provided for a demonstration project to be initiated between the CMS and NIH. This legislation may allow for licensure and for CMS subsequently to make funding decisions about islet transplantation under federal programs. In addition, this legislation allows CMS to cover medical care costs associated with islet transplantation for Medicare beneficiaries; for patients with type I diabetes, coverage will include patients with renal failure undergoing renal transplantation or previously having received a renal transplant.

In response to the MMA, NIH, NIDDK, and the National Institute of Allergy and Infectious Diseases (NIAID) issued a request for applications to create a clinical islet transplantation consortium. Those awards were made this past September, and the consortium had its first steering committee meeting in October. Materials related to the consortium are included in the meeting packet and will be reviewed by subsequent presenters.

ISLET TRANSPLANTATION OVERVIEW AND PERSPECTIVES

DHHS Multi-Agency Oversight of Islet Transplantation NIH Perspectives

Tom L. Eggerman, M.D., Ph.D., Director, Islet Transplantation Program, Division of Diabetes, Endocrinology, and Metabolism, NIDDK

Dr. Eggerman provided an update on efforts by the U.S. Department of Health and Human Services (DHHS) on islet transplantation and facilitated a discussion of current issues facing researchers and clinicians. In brief, islet transplantation is a treatment for patients with type I diabetes who receive injections of islet cells procured from donors. Islet cells are injected through the portal vein; the cells implant in the liver and produce insulin in response to glucose levels. Immunosuppression is needed to prevent rejection for as long as the implanted islet cells are functional.

Four DHHS agencies NIH, CMS, the U.S. Food and Drug Administration (FDA), and the Health Resources and Services Administration (HRSA) interact and provide oversight for different aspects of basic preclinical and clinical research on islet transplantation (slide 3).

The NIH provides funding for these different types of research as well as data safety monitoring board oversight for clinical studies;

The FDA provides advice for clinical research and investigational product oversight in the form of Investigational New Drug (IND) applications, product licensure, and postmarketing followup;

The HRSA provides oversight for organ procurement, distribution, and transplantation outcome; and

The CMS determines coverage for new products and procedures and reimbursement rates, and, in the case of islet transplantation, will fund specific NIH transplantation studies involving Medicare beneficiaries.

The NIH supports basic research efforts in both academic and small-business settings (slide 4). This includes a multitude of human and nonhuman studies (especially rodent studies) involving stem cells, embryology, physiology, imaging, encapsulation and transplantation, and the Beta Cell Biology Consortium, which was established to better understand the development of the islet, including identification of potential stem cell precursors. A preclinical effort at the NIH headed by the NIAID and cosponsored by the NIDDK is the Non-Human Primate Immune Tolerance Cooperative Study Group (slide 5). This effort has resulted in the finding that there can be tolerance development with islet transplantation that obviates the use of long-term immunosuppression. Another NIAID-NIDDK preclinical collaboration that will be funded in 2005 is the Immunobiology of Xenotransplantation Consortium, which will focus on porcine transplantation and rodent-porcine islet transplantation into nonhuman primates (slide 6).

Clinical efforts on islet research and transplantation include the Immune Tolerance Network, which sponsored the multicenter Edmonton trial and other clinical islet transplantation studies (slide 7). It is cosponsored by the NIDDK and the NIAID. The NIDDK also is sponsoring individual investigator clinical studies.

The Islet Cell Resource Centers, cosponsored by the NIDDK and the Juvenile Diabetes Research Foundation (JDRF), provide human islets for clinical and basic research (slide 8). The lead institute/center is the National Center for Research Resources (NCRR). The program includes 10 centers in the United States whose analyses include product quality and clinical outcomes and who collaborate with the UNOS to improve coordination of donor data. In addition, the Clinical Islet Transplantation Consortium (CITC), cosponsored by the NIDDK and the NIAID, was established to facilitate cooperative clinical trials using new approaches in islet transplantation (slide 9). The CITC had its first meeting in October 2004 and will focus on clinical and mechanistic studies, with five funded clinical sites and a coordinating center. As part of the mandate issued by the MMA, the NIDDK is implementing an investigation of islet transplantation in Medicare beneficiaries for whom the cost of pancreas islet isolation and usual medical care costs will be covered by Medicare (slides 10-11). This investigation is being implemented through the CITC and will include Medicare patients with renal failure or those who have received a renal transplant. The need for additional centers for the CITC beyond the five that currently are part of the consortium is anticipated to accrue a sufficient number of patients. Workshops are planned to identify the major questions and approaches for this clinical investigation, and the outcome will be the safety and efficacy of islet transplantation in Medicare beneficiaries and the consideration of Medicare reimbursement and FDA licensure.

To collect, analyze, and communicate data on all islet and beta cell transplants performed in North America, the NIDDK initiated and funded the Collaborative Islet Transplantation Registry (CITR) in 2001 (slide 12). Currently, there are 17 North American centers providing data, and five European sites are being added through the JDRF. The first CITR annual report was produced in September 2004 and contained data from 158 islet infusions.

FDA Oversight: Pancreatic Islet Cells
Joyce Frey-Vasconcells, Ph.D., Acting Deputy Office Director, Office of Cells, Tissue and Gene Therapies, Center for Biologics Evaluation and Research, FDA

Dr. Frey-Vasconcells provided an overview of FDA responsibilities and authority regarding pancreatic islet cell regulation and licensure (slide 2). In September 2000, the FDA notified transplant centers that the agency has regulatory authority over islet cell therapy and that the centers are subject to licensure under section 351 of the Public Health Service (PHS) Act. In addition, products for islet transplantation meet the definition of a drug and, therefore, are subject to compliance with the Food, Drug and Cosmetic (FDC) Act. A new regulatory approach for cells and tissues has been established that (slide 3)

Provides a unified regulatory framework

Provides greater flexibility and innovation in this field of medicine

Provides a tiered regulatory approach, with the level of regulation proportional to the degree of risk

Provides clarification of risk: low-risk products are defined as tissues and regulated under section 361 of the PHS Act; high-risk products require preapproval and are regulated under section 351 of the act or by the FDC.

New tissue regulatory rules the Donor Eligibility and the Good Tissue Practices (GTP) rules have been issued and will take effect on May 25, 2005 (slides 4-7). The following rules define what the FDA considers a cell therapy, a tissue, and cellular and tissue-based products (HCT/Ps):

Rule *21CFR 1271.3(d)(1)* provides a definition of cell therapy, and tissue as "human tissue derived from a human body and intended for transplantation into another human as defined in 1270.3(j)."

Rule *21CFR 1271(d)(2)* further defines human cells, tissues, and HCT/Ps as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Vascularized human organs for transplantation are not HCT/Ps."

Rule *21CFR 1270.3(j)* defines human tissue as any tissue derived from a human body "(1) intended for transplantation to another human for the diagnosis, cure, mitigation, treatment, or prevention of any condition or disease, (2) recovered, processed, stored, or distributed by methods that do not change tissue function or characteristics, (3) is not currently regulated as a drug, biologic, or device, and (4) excludes kidney, liver, heart, lung, pancreas, or any other vascularized human organ."

To determine the criteria for distinguishing between a tissue and a regulated article, the FDA determined that a product is a tissue if it is minimally manipulated; for homologous use only, based on advertising, labeling, or the intent of the investigator; not combined with a drug or a device; and its activity is not systemic or metabolic, unless it is for autologous or reproductive use (slide 8).

Pancreatic islet cells fall within the FDA criteria for cell therapies because they fit the definition of HCT/Ps and therefore are regulated under section 351 of the PHS Act, are more than minimally manipulated, their activity is systemic and metabolic and most islet transplantation is allogeneic, and they are not a vascularized organ (slide 9). There currently are 39 active IND applications for pancreatic islet cell therapy products that will require FDA licensure through the biologics license application (BLA) process (slides 10-11).

Discussion

Dr. Frey-Vasconcells noted that additional slides on the regulatory process were included in participant packets but were not presented at this time. These have been placed on the NIDDK

DMICC meeting Web site at *www.niddk.nih.gov/federal/dmicc/meetings.htm*. A participant asked if the studies discussed by Dr. Eggerman include products that adhere to the new regulations regarding packaging and other requirements. Dr. Frey-Vasconcells responded that the cell therapies in research trials of INDs are required only to state that the agent is only for investigational use. After the trials, if the agent is to be licensed, it will need to meet the new labeling requirements.

CMS Perspective

Paul Olenick, Director, Division of Technical Payment Policy, Center for Medicare and Medicaid Services

Paul Olenick provided information on the MMA, which directed the Secretary of DHHS to have Medicare pay for the costs of the experimental pancreatic cell transplant program. This was unusual for CMS because it normally does not pay for experimental procedures. CMS fit reimbursement for pancreatic transplants into the normal payment system, which involves the Hospital Prospective Payment System. CMS determined which diagnosis-related group (DRG) these procedures would apply to and determined a reimbursement amount per procedure to isolate pancreatic islet cells for transplantation based on data from the isolation centers. In addition, CMS will pay a reasonable cost for acquisition, although no set amount is specified in CMS policies.

Last spring, CMS published proposed changes in acquisition costs, with final provisions published in August that took effect on October 1, 2004. This process will occur yearly so that proposed acquisition costs can be updated based on data for the past year. There remains the restriction that CMS cannot reimburse for patients in a trial unless they are Medicare patients. Among Medicare patients who receive kidney transplants, CMS will reimburse expenses only for 3 years following transplantation. Among comments received during the comment period for proposed reimbursement changes, CMS had many questions about the possibility of extending the 3-year reimbursement period. Changes of this nature must evolve from the legislative process rather than through internal CMS rule changes.

Discussion

Dr. Fradkin commented that the Modification of Diet in Renal Disease (MDRD) clinical trial was conducted jointly between NIH and CMS, and there may have been relaxation of requirements regarding Medicare eligibility. She asked for comments on this trial. Dr. Allen Spiegel, Director of NIDDK, added that the MDRD was a protein-restricted trial to see if protein restriction could delay end-stage renal disease (ESRD) and was completed in the early to mid-1990s. Mr. Olenick said he was not familiar with details of the trial, but it might be advantageous to determine if individuals at CMS or the Healthcare Financing Administration (HCFA) who participated in the MDRD could provide information on its relevance to Medicare eligibility. Dr. Spiegel added that Medicare eligibility is critical to designing trials in this population, in which there are limitations on the number of islets that are available and the accrual rate is limited, especially in a longer-term trial with the usual kinds of endpoints and a 3-year time limit for patient coverage through Medicare. Mr. Olenick reiterated that this has been

discussed in his agency, but the conclusion has been that coverage beyond the 3-year requirement is against the statute as currently written.

Update on HRSA/Organ Procurement and Transplantation Network (OPTN) Activities in Pancreas and Islet Transplantation

Laura M. Saint Martin, M.D., M.P.H., Chief Medical Officer, Health Resources and Services Administration, Division of Transplantation

Dr. Saint Martin provided an update of the HRSA oversight of the national OPTN. At present, there are 45 pancreatic islet programs. Earlier in 2004, the OPTN Board of Directors approved criteria developed by the OPTN Kidney and Pancreas Committee for islet program membership and also for requirements for physician and surgeon experience and training (slide 3). These significant decisions were made, although islet transplantation still is a relatively experimental procedure, to give patients as much information as possible on the options of whole-organ transplantation and islet transplantation.

Reporting requirements for islet programs are being developed; in the interim, islet programs are required to report every 6 months on patients transplanted, including information on whether the islets received are disposed through transplantation, whether they were transplanted into the patients to whom they were allocated, or whether they were discarded or used for another purpose (slide 4). The islet programs also must have adequate clinical and laboratory facilities as defined by the FDA and must document that they have a required IND application in effect. Other requirements include the existence of a collaborative relationship with a physician qualified to cannulate the portal system, and the isolation of the islets must occur in a facility with an FDA IND application in effect (slide 5). Additional criteria exist for programs in centers without a whole-pancreas transplant program. A few islet programs exist where there is not a whole-pancreas transplant program within the same center; such programs may be allowed to qualify if they have a demonstrated affiliation with a qualified whole-pancreas transplant program.

Currently, all patients who are potential recipients of organ transplants must be listed on the computer waiting list, including islet transplant recipients (slide 6). As of November 5, 2004, the waiting list contains 1,648 pancreas candidates, 2,461 pancreas and kidney combined candidates, and 324 islet candidates. In 2003, only 502 whole-pancreas transplants were performed and 870 combined kidney-pancreas transplants were performed (slide 7). Data on islet transplantation were not collected in 2003.

Dr. Saint Martin presented information on the OPTN allocation algorithm that gives local priority for whole-organ transplantation but has approved variances for granting higher priority for local allocation of pancreata for use in islet transplantation (slides 8-12). Under the new pancreas allocation algorithm, priority is given based on length of time on the waiting list, with the highest priority given to zero-mismatched and highly sensitized candidates (i.e., Panel Reactive Antibody [PRA] ≤ 20). If there are no zero-mismatch candidates, the local isolated pancreas or combined kidney-pancreas or combined cell-organ-islet candidates receive the next

highest priority; if the pancreas is still not accepted by a program, it is allocated based on donor age and body mass index (BMI). The algorithm for age and BMI is as follows:

Donor age ≤ 50 years AND BMI ≤ 30 kg/m^2
Regional isolated or combined kidney-pancreas; then
National isolated or combined kidney-pancreas; then
Facilitated isolated or combined kidney-pancreas; then
Local, then regional, then national islet; then
Research.

Donor age > 50 years OR BMI > 30 kg/m^2
Local, then regional, then national islet; then
Regional, then national, for whole-pancreas transplantation; then
Research.

There still are ongoing issues and concerns, despite the new policies (slides 13-14). The allocation priority for whole-organ transplants may mean that there are fewer ideal pancreata available for islet transplants when other factors are considered, such as the time it takes to offer the organ and local need. In addition, cost and reimbursement issues are involved in all procurements by OPOs of pancreata and in patient transplants. Although whole-pancreas transplantation is an accepted therapy, no substantial comparisons have been done between islet transplantation and whole-pancreas transplantation. Another issue is developing a system to inform patients and families about the benefits and barriers to whole-pancreas versus islet transplantation.

ISSUES FOR DISCUSSION

ISSUE #1: Islets as a cellular therapy versus tissue versus organ

Dr. Eggerman began the discussion by noting that the FDA considers pancreatic islet cells a cell therapy; HRSA designates them as an organ. These disparate definitions have implications for use, collection, procurement, allocation, and cost. In particular, a designation of "tissue" instead of "organ" by the FDA and HRSA would be most beneficial for most considerations regarding islet transplantation. Dr. Frey-Vasconcells reiterated that pancreatic islets are viewed as neither tissues nor organs, and there is no way under current regulations to designate them as such. As a cell therapy, islet cells are regulated; this does not appear to have impeded progress in the field. Dr. Eggerman noted that islet cells are highly vascularized *in vivo* but lose this characteristic during processing; after transplantation, they become vascularized again. Dr. Frey-Vasconcells again stated that the FDA regulates products given to patients and designates them only at that point; at the point of transplantation, islet cells are not vascularized.
Dr. Jim Bowman, CMS, emphasized that it is important to maintain the allocation process under the jurisdiction of HRSA and OPTN, and that nothing recommended in these meetings should interfere with or impede progress of planned studies on pancreatic islet transplantation. It is important to keep in mind safety versus access issues. Registration as a tissue bank is not

characteristic of all OPOs, and there are consequences if OPOs must contain a tissue bank. This issue will come to the forefront if islet research results in treatment success and islets become viewed by the medical and consumer communities as a commodity. Dr. Bowman's opinion is that this issue should be addressed as early as possible so that planned studies can proceed without impediments caused by allocation problems.

Dr. Eggerman summarized that, from these discussions, it appears that the manner in which the FDA and HRSA view the process is appropriate, that no changes are needed at this time, and that progress will not be impeded. Participants added that, at this point, accruing patients to trials is not a problem and shortages do not exist. Once licensure is given, however, there will be the potential for product shortages. The HRSA has experience with organ shortages and can use that experience to address islet shortages if they emerge as an issue.

There were differing opinions among participants on whether it is advisable to classify islets as tissues. Some participants felt there would be no benefit in classifying islets as tissues; others felt that islets should be classified as tissues because the FDA would regulate them and there is a strong safety component in the FDA's regulatory process. A participant asked if someone could address how the May 2005 regulations will affect the IND process, particularly whether an OPO that has not been registered under the first of the three regulations *Rule 21CFR 1271.3(d)(1)* as a tissue bank can provide islets for the study. A participant stated that, if the FDA designates islets as tissues, its only control would be over safety regarding transmission of communicable diseases; the FDA will not have control over the quality of islets, the data, or other parameters. Dr. Frey-Vasconcells responded that the OPOs would have to meet the tissue rules that apply to them for the processes they do at the time islets are licensed. Tissue rules do not apply to investigational products. For the OPOs, if they are procuring a cell therapy, they must register unless the procurement is related to products under investigation. This would not impede the conduct of studies on islet transplantation, although there would be more regulation once the investigational product is licensed. OPOs can register with the FDA online. Preventing the transmission of communicable disease is the only safety control under section 361, and any additional safety controls or safety issues fall under section 351. In summary, OPOs that retrieve tissue must register and only must adhere to the parts of the GTPs that apply to their processes.

One issue that needs clarification is the impact of designating islet cells on the cost of procurement and reimbursement by Medicare. Depending on whether islets are called cells, tissues, or organs, the cost reimbursed by Medicare can range from $5,000 for cells to as much as $25,000 for organs. Dr. Fradkin questioned whether organs that are part of the Medicare Demonstration Project would be reimbursed at the higher rate even though only the islets or whole pancreas are being used for the project. This was affirmed in discussions among CMS attendees but still leaves open the question of how to determine reimbursement for less-than-ideal organs. In addition, CMS often pays a reduced price, not because of a tissue designation, but because the organs would not otherwise be used by the OPO. Dr. Fradkin pointed out that one way islets get used is from organs that have vasculature that make them unusable for whole-organ transplantation. A participant added that many of these questions should be addressed at the upcoming OPTN/UNOS meeting in January.

ISSUE #2: The development of the special organ product (cells or tissue derived from organs) category for transplantation

Dr. Jim Burdick, Director of the Division of Transplantation, DHHS, provided information on a proposal for joint interagency regulation of living organ products. This will address many of the issues regarding islet transplantation and the problems of classifying islets within existing federal regulations and oversight. Removal of the pancreas for islets utilizes a considerable portion of the OPO's resources. It is not just the operation, it is all of the steps that lead up to the operation and the expense of distribution for transplantation. Understanding who will pay for these procedures is critical to the process, and ensuring that everyone involved defines the materials in a consistent manner is important for both patients and OPOs. A participant noted that these also are important for research on islets; it is important to have some means of support to help with the costs of research. A CMS participant stated that CMS will pay for the cost of the whole organ even if only a portion is used. There may be differences among OPOs, but the amount paid generally is about $25,000 per organ. CMS agrees that there are additional costs for the OPOs other than procuring and distributing organs.

Dr. Gilman Grave asked if there were patient data on the number of pancreata needed for the number of islet transplants performed. Does it generally take more than one pancreas to collect enough cells for one patient? A participant responded that the majority have been two or more, with a minority of patients needing only one pancreas. The problem is the imperfect process for extracting the million or so islets that exist in a normal pancreas. The issue of collection is being investigated by the NCRR to improve yields without compromising cell efficacy. Also, there are problems regarding the transplantation procedure itself. Many of the islets that are infused do not implant and subsequently are inactive and then are lost. By improving the process of collection and storage, the number of pancreata needed to complete transplantation can be reduced.

Dr. Burdick commented that there are two key issues to address. The first is cost, which can be settled by establishing agreements among the agencies involved in organ procurement and distribution. There may be an alternate way to address islet transplantation. The second issue is that of safety versus access, as stated before. This is a fundamental issue, but it is important to focus first on the availability of organs. Dr. Fradkin recommended that Dr. Burdick's draft be circulated to the participants for discussion at future meetings.

ISSUE #3: Resolution of issues related to credit for OPOs when pancreata are used for islets (with passage of the Pancreatic Islet Cell Transplantation Act of 2004)

In Section 2 of the Pancreatic Islet Cell Transplantation Act of 2004, pancreata procured by an OPO and used for islet cell transplantation or research are counted for purposes of certification or recertification. The DMICC will report on progress in this area for the 2005 DMICC Annual Report. Issues related to islet cells for transplantation or research have been discussed in the

context of issues 1 and 2, above. At a minimum, the adequacy of federal funding for taking advantage of scientific opportunities related to pancreatic cell transplantation can be enhanced by crediting OPOs for the use of islet cells in research. Other issues include adequacy of supply of pancreata. Crediting OPOs for using islet cells for research should serve as an incentive to these groups to make an effort to distribute as many of the procured pancreata as possible.

ISSUE # 4: Update on the Islet Transplantation Consortium

Nancy Bridges, M.D., Chief, Clinical Transplantation Section, NIAID, provided an update on the islet transplant consortium, which has granted five awards to investigators to create a 5-year agenda and to develop strategies for moving the islet field forward. The five investigators are Drs. Bernard Hering at the University of Minnesota; Olle Korsgren at Uppsala University in Sweden; Ali Naji at the University of Pennsylvania; Camillo Ricordi at the University of Miami; and James Shapiro at the University of Alberta, Edmonton. In addition, Bill Clark at the University of Iowa will head a consortium coordinating center. The first steering committee meeting was held recently to develop scientific goals for the consortium, including

To achieve adequate islet mass from a single donor;

To identify optimal assays of islet potency;

To identify the best outcome measures for clinical studies of islet transplantation; and

To identify patients and conditions that benefit the most from islet transplantation.

The proof-of-concept has successfully been demonstrated by the Edmonton protocol, which indicates it is possible to transplant islets into human beings and have them become functional, although the approach is not yet perfected. The Edmonton protocol was innovative in how it treated the immunosuppression issue by developing a steroid-free immunosuppression regimen that included an investigational (at the time) agent, Sirolimus, to try to protect the islet graft from rejection.

Evidence suggests it is not just alloimmunity that results in the loss of islets and that the innate immune system also is a significant problem. Three consortium investigators have identified approaches to target innate immunity after islet transplantation. Dr. Hering has a protocol that uses an investigational agent, deoxyspergualin, along with a tumor necrosis factor (TNF) blocker, Etanercept; Dr. Korsgren and his group in Sweden have very good preliminary data using low molecular weight dextran as an anti-inflammatory agent along with melagatran, an anticoagulant agent; and Dr. Ricordi is investigating two anti-inflammatory/anti-apototic investigational agents, lisofylline and exenatide. These studies exemplify the significant focus on the innate immune and coagulation systems in trying to improve both islet engraftment and islet survival. Targets of innate immunity aside from TNF include a cascade of cytokines that results in a nonalloimmune response. Other studies, including one by Dr. Naji, have produced data in a nonhuman primate model that show that simultaneously attacking both the T-cells and B-cells with Rituximab can result in tolerance or near-tolerance after islet transplantation; human trials are needed to confirm this approach. The fifth grantee, Dr. James Shapiro, is investigating

a costimulatory blockade with the use of LEA29Y, an investigational agent that blocks some poststimulatory interactions. This, too has been shown to be promising in animal studies.

Discussion

A participant asked what outcome measures are being designated for islet therapy. Dr. Bridges responded that insulin dependence will be monitored as a primary outcome in all trials, and microvascular complications will be monitored as a secondary outcome in some trials. Dr. Fradkin added that Dr. Eggerman is planning a meeting of investigators who have been involved with some major diabetes clinical trials and epidemiological studies to examine the kind of power that might be expected for certain outcomes. After determining issues of power and outcomes, input will be sought from the FDA and CMS. Based on the results of these trials, it is anticipated that product licensing will occur. This will have implications for standard treatments and public awareness.

ISSUE # 5: Update on the Medicare Islet Transplantation Clinical Investigation

A workshop is planned to better define the type of clinical trial approach that might be implemented to provide more information on Medicare islet transplantation. Input will be sought from experts in diabetes and transplantation and from colleagues in Europe who have been heavily involved in islet-renal transplantation. This will not be a typical study with thousands of patients; at most, hundreds of patients will be involved.

A subcommittee will determine potential approaches and address such details as the means for adding additional trial sites. The task is complicated by the facts that the harvesting and processing of islets are involved, and the postoperative care of patients is crucial to ensuring successful transplants. Thus, patients must be located at other sites; then costly, complicated details of their travel, transplant, and postoperative and ambulatory care must be arranged and managed. Limiting the number of sites that produce the islets and transplanting the islets to patients at multiple clinical sites may minimize variables. The Edmonton trial, in which good results were achieved in some cases and bad results were achieved in others, exemplifies the complicated nature of this type of trial.

Processes to be determined include

How islets are isolated,

Whether islets are cultured,

How islets are transported,

How islets are infused into the portal vein,

Patients' coagulation state at the time of infusion,

How quickly Sirolimus and tacrolimus levels are increased,

How long patients spend in the recovery room and the ICU, and

Gauging the degree of autoimmunity and its role in the loss of function in transplanted islets.

The structuring of these processes over the next 5 years will determine whether the desired results are achieved from the trial.

The pancreas transplantation legislation mandates that the DMICC report regularly on progress related to this effort. A subgroup of the DMICC will be created specifically to address the new tasks given to the DMICC under the pancreas transplantation legislation. Dr. Eggerman will lead this group, and relevant/interested member agencies and institutes (including the FDA, HRSA, NIAID, NCRR, and the Centers for Disease Control and Prevention [CDC]) should be represented. The group will meet regularly and report to the DMICC on progress in islet transplantation.

Items to be addressed in these reports include

An assessment of federal activities and programs related to pancreatic islet transplantation

The adequacy of federal funding for taking advantage of scientific opportunities relating to pancreatic islet cell transplantation

Available scientific opportunities

Unmet needs

Current policies and regulations that affect the supply of pancreata for islet cell transplantation

The effect of xenotransplantation on advancing pancreatic islet cell transplantation

Mechanisms for collecting outcomes data from existing islet cell transplantation trials

Implementation of multiagency clinical investigations of pancreatic islet cell transplantation

Recommendations for legislation and administrative action that would affect the supply of available pancreata

The group can determine the timing of the report to maximize its effectiveness.

Future updates of the patient registry will be standardized and enabled by the use of software packages. This will be accomplished particularly at the major centers and will facilitate the entry of additional patients into the registry.

ISSUE #6: The upcoming consensus conference on pancreas allocation for whole-organ and islet transplantation sponsored by the Kidney and Pancreas Transplantation Committee of the OPTN/UNOS on January 23-24, 2005

Dr. Saint Martin commented that one of the concerns that the OPTN/UNOS Kidney-Pancreas Committee has expressed is the ongoing representation of some of the islet concerns on the committee. The committee is considering having a representative with specific interest in islet transplantation join the committee to raise concerns and discuss issues brought forward at this meeting. A Consensus Conference on Pancreas Allocation for Whole Organ and Islet Transplantation will be held as a separate meeting, with recommendations to address allocation, procurement, data reporting, regulatory, and reimbursement issues.

Dr. Fradkin asked Dr. Saint Martin to review the consensus process and how OPTN/UNOS will handle recommendations from the meeting. Dr. Saint Martin responded that the process is not like the NIH consensus process, and the recommendations will have to be presented to the full OPTN Kidney and Pancreas Transplantation Committee to determine which recommendations should become OPTN policy and which need further study. Recommendations will proceed through the regular committee deliberative process before being considered for implementation. Dr. Fradkin asked if the consensus conference would examine changes to the new pancreas allocation algorithm. Dr. Saint Martin indicated that the committee will review the algorithm and give it special attention. Input will be garnered from a wide spectrum of opinion leaders. The OPTN Kidney and Pancreas Transplantation Committee intends to designate one kidney-pancreas committee meeting per year specifically for examining pancreas and islet issues, which is a major step forward.

A participant asked if the issue of acquired pancreata that subsequently are discarded because of various matching problems and other issues will be discussed. Dr. Spiegel added that he has heard that there is more concentration on kidney transplantation than on pancreas transplantation, and this may be reflected in the makeup of the committees that are discussing these issues. He said he would like to see a group address these issues from an independent viewpoint by looking at the evidence that exists for pancreas-only versus pancreas-kidney or kidney-only transplantation to make scientifically sound decisions. Having the consensus conference is a good idea and will add to the knowledge base regarding pancreas or islet transplantation, but the decision to treat an individual patient must be based on the best available evidence.

Dr. Spiegel interjected that there must be a way to increase the number of people who receive transplants because many organs never make it into the transplant pipeline. A participant responded that geographical problems in the transplant milieu may be overcome if new ways to transport organs or extend their useable life are discovered.

Dr. Spiegel asked whether the current policy as outlined at this meeting would impede and retard the planned demonstration project or trials on islet transplantation. A participant affirmed this contention. Dr. Spiegel indicated that this, then, becomes the main barrier to be overcome in designing and conducting the trial. Dr. Fradkin responded that two significant barriers appear to have been overcome. The first is the issue of reimbursement; the second is the issue of

allocation, although issues of timeliness and geographic distribution still must be addressed. Dr. Spiegel added that placement of trial centers could address the geographical issue, and developing some variance mechanism that gives consideration in terms of islets could address the allocation issue. A participant said that variances have been implemented in some locations, and it seems that data from those locations would help address the potential benefits of using variances. Dr. Spiegel added that variances are issued by the OPTN. Dr. Saint Martin noted that the current policy for facilitated placement is 5 hours. After 5 hours of attempted placement without being placed for whole-organ transplant, the organ then may be allocated locally, regionally, or nationally, before being allocated for islet use and then finally for research.

A participant introduced the issue of the lack of data on the optimal time needed to procure and transplant an organ or islets. These data may be available from the OPOs, and some effort might be expended to see what can be gathered from these organizations. Dr. Fradkin mentioned that this data might be useful in developing policies on variances. For example, presentations by sources such as the demonstration project in Miami may answer some of the questions about collection and allocation. Dr. John Ridge of NIAID added that one of the largest pancreas transplant centers in the United States, in Minnesota, has a variance and may have some data regarding this issue, although the center completes only one-on-one studies and does not conduct controlled trials. A participant commented that there may be a benefit in looking outside the funded network to find groups with experience and data on variance.

NEXT STEPS

Dr. Fradkin summarized the mandate of the DMICC required by the pancreas transplantation legislation and stated that the DMICC will report on progress related to this effort. She proposed that Dr. Eggerman create a DMICC subcommittee to address the responsibilities related to promoting islet transplantation under the legislation with each of the member agencies and institutes that are relevant or interested in islet transplantation taking part and that this subcommittee should meet regularly and report back to the DMICC on progress. A participant commented that the FDA, HRSA, CDC, NIAID, and NCRR should be involved because the legislative mandate includes requirements that can best be answered by these agencies. Dr. Eggerman will take the lead in developing the concept of a subcommittee and will contact DMICC members for input. Dr. Spiegel thanked those in attendance, and the meeting was adjourned.