National Institute of Diabetes and Digestive and Kidney Diseases
Diabetes Mellitus Interagency Coordinating Committee

DMICC Meeting on Islet Transplantation

May 30, 2006
10:00 a.m.–1:00 p.m.

Natcher Conference Center
Conference Rooms E1/E2
National Institutes of Health Campus

Summary Minutes

WELCOME AND OPENING REMARKS

Judith E. Fradkin, M.D.; Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), Bethesda, Maryland

Dr. Fradkin welcomed members of the Diabetes Mellitus Interagency Coordinating Committee (DMICC), guest speakers, and guest attendees. She reviewed the status of current initiatives of the DMICC, including the Strategic Plan for Type 1 Diabetes Research that will be completed this summer after a final draft is circulated to the Interagency Committees (ICs) for comments. In addition, an evaluation report on special funding for type 1 diabetes is due to Congress in January 2007; Dr. Mary Hanlon from the NIDDK Policy and Planning Office will be developing the report and will be sending it to the DMICC member organizations later in the fall for review and comment. The evaluation will include important findings and accomplishments made possible by the program, progress reports for the major consortia and activities conducted with the special funding, as well as information such as bibliometric analysis of publications, surveys of the grantees.

PURPOSE OF MEETING/OVERVIEW OF PREVIOUS DMICC ISLET TRANSPLANTATION MEETING

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

Dr. Eggerman reviewed the agenda and explained that the previous DMICC meeting on islet transplantation was in November 2004; since that time, enough research and policy advances have occurred, to make the need for this update on islet transplantation significant. He

reviewed the background and funding issues regarding islet transplantation and the role of federal agencies involved in the procurement and research in this area.

NIH funds basic, preclinical, and clinical research; programmatic oversight for cooperative agreements; and Data and Safety Monitoring Board (DSMB) oversight for clinical studies. The U.S. Food and Drug Administration (FDA) provides guidance for preclinical research, investigational product oversight, product licensure, and postmarketing followup; the Health Resources and Services Administration (HRSA) provides oversight of organ procurement, allocation, and transplant outcome followup; and the Centers for Medicare and Medicaid Services (CMS) determines coverage of new products and procedures and reimbursement rates, and will provide funding for the Clinical Islet Transplantation (CIT) clinical studies involving Medicare beneficiaries.

A significant research effort has occurred on islet transplantation in the past few years. For example, the National Institute of Allergy and Infectious Diseases (NIAID) established the Immune Tolerance Network, a collaborative research effort that included the multicenter Edmonton protocol. NIH also supports single-investigator clinical studies on islet transplantation and the CIT Consortium has been established to facilitate cooperative clinical trials using new approaches in islet transplantation. The consortium currently has five clinical sites and a coordinating center jointly funded by NIAID and NIDDK.

NIH also supports research on islet transplantation through the following programs:

NIH supports basic research grants and consortia for basic and preclinical research.

- NIAID and NIDDK jointly fund a nonhuman primate immune tolerance cooperative study group.

- NIAID and NIDDK also fund a consortium for the immunobiology of xenotransplantation.

- The Islet Cell Resource (ICR) Centers are funded through the National Center for Research Resources (NCRR).

- The Collaborative Islet Transplant Registry (CITR), which collects data on transplants in North America, is operated and funded by NIDDK.

- NIDDK also supports the type 1 diabetes Rapid Access to Intervention Development (RAID) program, which supports necessary components in the development of products for transplantation.

CLINICAL ISLET TRANSPLANTATION CONSORTIUM UPDATE

Nancy Bridges, M.D., Chief, Clinical Transplantation Section, NIAID, NIH, Bethesda, Maryland

Dr. Bridges presented information on the CITC, including background information and a list of tasks conducted by the consortium. There are six grants and five clinical centers within the consortium. The goals of the CITC include obtaining licensure for an islet product for use in two target populations—persons with type 1 diabetes with severe hypoglycemic events and good kidney function and persons with type 1 diabetes who have undergone kidney transplantation, which is part of the Congressional mandate. A broader goal of the CITC is to continue to move the field of islet transplantation forward with innovative approaches.

Dr. Bridges described how licensure and innovation are brought together in the consortium. Incorporating these two approaches into one consortium was a significant challenge. The approach was to establish five North American clinical trials on islet transplantation in persons with type 1 diabetes and normal renal function. One of the five multicenter trials is investigating "standard therapy" (i.e., based on the Edmonton experience); the other four single-center trials are investigating innovative therapies. In addition, there will be one North American multicenter trial in persons with type 1 diabetes and prior kidney transplantation and two Nordic Network trials in the same populations, although the Nordic Network trials will not be involved in licensure. Dr. Bridges presented slides describing the trial protocols and designs that are used for each arm of the trials. The primary endpoint for the Licensure Trial includes HgbA1c less than 6.5 percent and freedom from severe hypoglycemia at one year from the initial transplant; the secondary endpoint includes insulin independence at Day 75 following the first transplant. The primary endpoint for the Innovation Trials includes insulin independence at Day 75 following the first transplant, with multiple secondary endpoints. The overall purpose of these trials is to determine if better care at the beginning of the process of islet transplantation will improve the chances for a successful transplant. Because islet transplantation is an established procedure in Scandinavia, the Nordic trial (CIT-01) explores an innovative strategy incorporating the use of the investigational agent LMWDS **[Author: Is LMWDS = low-molecular-weight dermatan sulfate?]** for islet transplantation in subjects with and without a history of prior kidney transplantation. These trials use the same manufacturing standards, insulin/endpoint criteria, and endpoints as the North American study.

Dr. Bridges provided a list of milestones completed by the CITC in the first two years. These include:

- The seven protocols are complete;
- An islet-specific Toxicity Table is complete;
- Mechanistic and metabolic study designs are completed, and core labs have been established;
- There has been DSMB approval for all trials; and
- Three sites have made Institutional Review Board (IRB) submissions, with the remainder anticipated within 30 days.

There have been meetings with the U.S. FDA to develop a regulatory strategy for islet transplantation. Other regulatory highlights include the completion of a Drug Master File, Manufacturing Batch Record, and Good Manufacturing Practice (GMP) site evaluations. In addition, the investigational brochure is near completion.

Dr. Bridges described the clinical trial infrastructure and subcontracts with Covance for clinical trial monitoring and legal entity in Europe and a subcontract with PPD for clinical trial monitoring in North America as well as for international specimen tracking. Industry partners have been brought on board and include one finalized CTA with Nippon-Kayaku of Japan; others are in various stages of review with BMS, PK Chemicals, Roche, Diakine, Eli Lilly, Genentech, Medtronic, and Genzyme.

In summary, Dr. Bridges reported that enrollment of patients is anticipated for late this summer (2006) or early fall.

Discussion

Dr. Fradkin thanked Dr. Bridges and Dr. Eggerman for the amount of effort in planning and implementing the CITC. She asked if meeting participants had questions.

A participant asked if the timeline described could be met. Dr. Bridges replied that time is always an issue in planning for such a large project, but every effort is being made to keep things on track.

A participant asked if there are targets for age, race, or gender. Dr. Bridges described the trial design as including ages 21 to 65 years, although the youngest patients have to meet the age requirement and a requirement for duration of disease (i.e., well-established disease and failed medical management). Race and ethnicity have been addressed by the placement of trial centers in areas that should include significant numbers of ethnic and racially-diverse populations. There is, however, no stratification by race or ethnicity. Dr. Eggerman added that in small trials, it is difficult to know if there are enough people needing islet transplantation to guarantee the types of racial and ethnic participation one would see in large clinical trials.

Dr. Michael Engelgau, by teleconference phone, asked about the need for a consistent supply of islet cells for research. He asked how the issue of stem cell research relates to these trials. Dr. Bridges responded that this is not an issue for the current trials. Dr. Fradkin added that research on beta-cells is a major focus of research, and supply is always a consideration in new research efforts. Dr. Bridges added that if just the amount of pancreata that are discarded could be recouped for islet isolation, there would not be a shortage of islets for research. It is thought that approximately 4 pancreata will be used for each individual receiving an islet transplantation, creating a significant problem in islet research and clinical trials.

To a question from another participant, Dr. Bridges commented that protocols for validation and characterization will be the same across all the trials. There will be two types of analyses

for each trial. One will be to determine if the primary endpoints are being met in the trials, but this will not necessarily lead to licensure. It is the individual centers that will be licensed, and they will have to meet criteria showing that the center favorably compares to the other centers, which may lead to licensure.

NIH-CMS ISLET AFTER KIDNEY TRIAL (IAKT) UPDATE
Dr. Eggerman

Dr. Eggerman described the protocol of the IAKT, which was congressionally mandated and would cover Medicare beneficiaries. Medicare will reimburse for the cost of the pancreas, islet isolation, and usual medical care related to the transplantation. Dr. Eggerman explained reimbursements would be implemented through the CITC sponsored by NIAID and NIDDK. A workshop was held in February 2005 to identify major questions and approaches that should be used, and the plan was to include Medicare renal transplant patients in an islet after kidney transplant protocol. The planned outcome is to determine the safety and efficacy of islet transplantation in these Medicare patients, attempting to obtain Medicare reimbursement approval and FDA licensure.

Dr. Eggerman described the prospective, multicenter, controlled, randomized phase III trial comparing the benefit of islet transplantation versus insulin medical therapy in kidney transplant recipients with type 1 diabetes. He provided information on randomization for 65 patients in two arms, agents used in each arm of the trial, and the protocols to be followed. The primary endpoint is the proportion of patients with both an HbAlc $\leq$ 6.5 percent and an absence of severe hypoglycemic events at 1 year after the first islet infusion, or a reduction of HbAlc of at least 1 percentage point and an absence of severe hypoglycemic events at 1 year after the first infusion. Secondary endpoints include quality of life, various measures of metabolic control, and various renal measures including biopsy, cardiovascular effects, diabetic neuropathy, vision, and cost of care.

The clinical trial and islet products will be regulated by the FDA's Center for Biologics Evaluation and Research, and the regulatory efforts are being made by the Division of Allergy Immunology and Transplantation (DAIT) within NIAID. Meetings with the FDA to discuss protocols have occurred in August and November 2005, with FDA submission planned for June 2006. DSMB meetings were held in September 2005 and April 2006, with patient accrual expected by late summer 2006.

PANCREAS PROCUREMENT COST ISSUE IN ISLET TRANSPLANTATION
Drs. Eggerman

Dr. Eggerman presented background on the costs of islet transplantation. In the past, most islet centers made arrangements with their local Organ Procurement Organization (OPO) regarding the cost of pancreata used in islet transplantation. These costs often varied from $5,000 to $15,000 and usually represented the additional marginal cost of procuring the pancreas when other organs were isolated and charged their usual costs. A few OPOs

charged a full clinical pancreas organ charge, especially if the organ was obtained from somewhere other than the local OPO. In all cases, if the islet isolation was unsuccessful, a charge representing the cost that would occur if the pancreas was intended to isolate islets for basic research was levied, often approximately $5,000. Because islet isolation is only successful approximately 50 percent of the time, in contrast to approximately 90 percent for organs used for whole organ transplants, most islet transplant patients require two islet transplants to achieve insulin independence. This results in as many as four pancreata being required to make a single patient insulin independent. In addition, because islet transplantation is still a research procedure, there is little or no third-party reimbursement as there is for whole organ transplants. Another factor restricting islet transplantation is the human and infrastructure resources required for FDA compliance, as human islets are an FDA-regulated product. Whole organs used in transplantation, in contrast, are not regulated by the FDA as licensed products. Dr. Eggerman also described restrictions inhibiting the use of many potentially viable pancreata for islet transplantation. These restrictions include limits on pancreata from older, obese patients and delays in obtaining and processing pancreata. These restrictions result in the majority of potentially useful pancreata being discarded.

Dr. Eggerman related the recently-released CMS directive indicating that the cost for pancreata used in islet transplantation should be based on the shared cost of procuring the organs. This full charge is applicable to any pancreas for which the intent is to use the islets clinically at the time of pancreas procurement. This directive profoundly increases the cost of procuring islets. In most cases, the cost of a pancreas used for whole organ transplant is $25,000 to $35,000. To treat an average single patient, four pancreata are needed, thus, the cost of organ procurement for islet transplantation has increased from $20,000–$70,000 to $100,000–$140,000. Many islet transplant programs have either significantly reduced their activity or eliminated their programs entirely because of the cost increase.

Dr. Eggerman described the conflicting priorities that the CMS directive has on islet transplantation research. Congress mandated funding research in islet transplantation, but the CMS directive limits the amount of research possible with current funding. He said two questions must be addressed to allow the proper balance between islet research and their use in the clinical setting: (1) At what point in the islet isolation procedure should “intent” (clinical vs. research) be determined?, and (2) How should pancreata used for islet transplantation be charged compared to other organs?

Dr. Eggerman recommended the following to address these questions.

- It is recommended that “intent” should be determined after islets are isolated and evaluated, rather than at the time of organ procurement.

- It is recommended that, when a pancreas is procured for islet isolation, the cost should be determined by the marginal additional cost of obtaining the pancreas. In this way, research can continue to determine whether or not islet transplantation is safe and efficacious for licensure.

- If licensure is obtained for the use of islets for human transplantation, full organ costs should be implemented for pancreata that yield transplantable islets. A larger number of islet transplants will then likely occur, resulting in higher percentages of pancreata being used and decreased costs of other organs being transplanted.

Discussion

Dr. Garfield asked what has happened in the past 20 years to change the approach on intent for islet transplantation. Dr. Eggerman responded that, historically, the rate of insulin control after one year was only approximately 10 percent. After the Edmonton experience, it was shown that the success rate could be higher. The low success rate before Edmonton was attributed to the types of immunosuppressants used with islets. Dr. Garfield followed up by asking if immunosuppression is a concern for islet transplantation in patients who are on immunosuppression agents following previous renal transplantation. Dr. Eggerman replied that this is an issue, but it is hoped that these patients would be kept on immunosuppression because the renal transplant should take precedent.

CMS PERSPECTIVE ON PANCREAS PROCUREMENT COSTS

Mark Horney, CMS, Department of Health and Human Services (DHHS), Baltimore, Maryland

Mr. Horney provided handouts of the CMS *Federal Register* notices dated August 11 and August 12, 2004, on "Pancreatic Islet Cell Transplantation in Clinical Trials." He described the handouts and said that CMS is mandated by Congress to reimburse appropriate costs for islet transplantation, which is done by pass-through reimbursements. He provided background on the reimbursement policy of CMS, which, in the past, included some confusion about reimbursements for islets. Recently, a conference on islet transplantation brought to the CMS's attention the fact that pancreatic organ procurement costs as much as other organ procurements. Data was collected and compiled to develop a more coherent policy for pancreatic procurement and islet isolation reimbursements. Some of the original estimates may have been high, but this is based on the best available evidence at the time.

Mr. Horney described the revision in 2005 to the provider reimbursement manual that OPOs and transplant centers must pay in full for islet isolation, which is currently $18,848 per islet isolation. It was noted, however, that it generally takes at least two procedures to complete the isolation, which makes the cost of isolation very high. Importantly, according to the Social Security Act, CMS is allowed only to pay for Medicare costs, not the costs of other payers. Mr. Horney said that CMS is paying the Medicare share of islet procurement and isolation but understands that this is not the full cost.

Discussion

Dr. Fradkin asked how cornea procurement relates within these regulations. Mr. Horney replied that cornea is a tissue and islet cells are treated as an organ, even though the transplanted islet cells are a tissue. Dr. Eggerman asked if the full cost of islet isolation is

paid only for the islets that are infused, or does the cost include the procurement and processing of the pancreas also? Mr. Horney said that the $18,848 is only for the infusion of the isolated cells.

Dr. Eggerman asked what would happen if a patient was admitted with the intention of receiving islets but the islets are found not to meet release criteria. Mr. Horney replied there are rules on that but he would need to consult with others in his office to give a clear answer. He added that these patients would have a different Diagnosis Related Group (DRG) than for a completed infusion, and this would probably result in a lower reimbursement. Dr. Bridges provided additional information on CMS regulations, which in this case would depend on which procedures are completed. This is one of the problems in islet research—if facilities are not receiving adequate reimbursement, they will not participate in the research. Dr. Bridges added that if islet research is to be mandated, there has to be a way to find a cost-effective way to do it so more research institutes participate.

Dr. Fradkin asked if other transplant policies are the same or different than that of islet transplantation. Mr. Horney responded that all transplants are handled the same, to which Dr. Fradkin asked if islets could be handled differently than other transplants. Dr. Jim Burdick presented a perspective on transplant costs and allocations that results in multi-organ procurements dividing the costs equitably among groups that use the organs. For example, some organs, such as the pancreas, do not cost as much to remove as organs such as kidneys or hearts. Mr. Horney said that according to allocation of costs on an OPO cost report, it does not matter where the organ is going, but simply that it is an organ. A bill goes to the transplant center, regardless of whether it is for a whole pancreas or just islets. Dr. Burdick commented that much of the cost is in securing the organ, doing the assessments of organ suitability, and getting the organs ready for transplant. If, in fact, this is a majority of the cost, costs should be divided among all the procured organs, making pancreata less expensive. Mr. Horney commented that Medicare only pays for the costs it incurs.

Dr. Burdick added that he would like to discuss the concept of "intent to transplant" versus the actual transplantation. The concept applies to islets because suitable islets are not recognized until farther along in the process than that of other organs. Mr. Horney described "intent to transplant" as occurring when surgeons are removing the organs; even if the organ (e.g., kidney, liver, or heart) is not suitable, there are still allocated costs for these procedures, although it is not directly billed to the OPO. These costs get placed into the overall expense of procuring the next organs, which makes the overall cost increase.

After a lengthy discussion of the "intent to transplant" issue, Mr. Horney stated that the discussion heard today would be taken back to his administrators at CMS to discuss possible changes in regulations that should be considered to alleviate the problem. Because the islet transplantation is a statute issue, change would have to be effected through the regulatory process. Dr. Bridges commented that these issues don't just affect Medicare beneficiaries because private-payer systems often use the same guidelines as Medicare for non-Medicare patients.

Dr. Fradkin added that this issue might be better addressed by bringing together all interested agencies and offices within DHHS. Discussing this issue might result in a more acceptable solution than if private groups pressure the U.S. Congress to change the regulations.

HRSA PERSPECTIVES ON ISLET TRANSPLANTATION INCLUDING THE PROPOSED SPECIAL ORGAN PRODUCT DESIGNATION

Jim Burdick, M.D., Director, Division of Transplantation, HRSA, DHHS, Rockville, Maryland

Dr. Burdick provided a handout on the "Joint Interagency Regulation of Living Organ Products (v.3Jun04)" that proposes a new mechanism for Federal oversight of materials obtained from deceased donors that do not meet the current definition of either an organ or a tissue. This regulation directly relates to islet cell transplantation research. The proposal would establish a new classification for complex living materials derived from whole organs: "Living Organ Products (LOPs)." When LOPs are in the research phase of development prior to FDA licensing, they would be designated as "Investigational Living Organ Products (ILOPs)." Dr. Burdick described the specific interests and oversight responsibilities of the FDA, HRSA, CMS, and NIH. This new process should clarify the roles, responsibilities, and funding issues for each of the Federal agencies involved in islet procurement, research, and transplantation. For example, NIH will fund basic research and clinical studies involving LOPs, and establish DSMBs to oversee clinical trials. The proposal also includes division of responsibilities for retrieval, processing, allocation, and data submissions related to the LOP.

Discussion

After a discussion of the proper course to take for resolving interagency issues, Dr. Fradkin suggested that the DMICC is where issues regarding islet transplantation should be resolved. She reiterated that DHHS, CMS, HRSA, and NIH representatives should meet together to work on interagency issues. This will move this issue to a higher level of resolution.

DMICC ANNUAL REPORT: ADDRESSING THE PANCREATIC ISLET CELL TRANSPLANTATION ACT OF 2004

Mary Hanlon, Ph.D., Health Science Policy Analyst, NIDDK, NIH, Bethesda, Maryland

Dr. Hanlon reviewed the Pancreatic Islet Cell Transplantation Act of 2004 (P.L. 108–362), which mandates that the DMICC annual report include an assessment of the Federal activities and programs related to pancreatic islet cell transplantation. The DMICC met this Federal mandate, Dr. Hanlon reported, by including a section on islet cell transplantation in the FY2005 DMICC annual report that was submitted this spring. The report may be viewed on the DMICC website at www.niddk.nih.gov/federal/dmicc/annual.htm.

Dr. Hanlon reviewed the main points of the 2005 report. The law mandates that the DMICC address seven items with respect to progress in islet transplantation. The areas, and the assessment of the current status of progress in the areas, included the following:

- **Adequacy of Federal funding for taking advantage of scientific opportunities**—DHHS is vigorously pursuing scientific opportunities in the field of islet transplantation.

- **The effect of xenotransplantation on advancing the field**—The Immunobiology of Xenotransplantation Consortium has two projects investigating islet transplantation.

- **The effect of the United Network for Organ Sharing (UNOS) policies regarding pancreas retrieval and islet cell transplantation**—The Organ Procurement and Transplantation Network (OPTN) has a new pancreas allocation algorithm to increase the use of pancreata that otherwise might not be used for transplantation. The Kidney and Pancreas Transplantation Committee has split into two separate committees: Kidney Transplantation and Pancreas Transplantation Committees.

- **Policies and regulations affecting the supply of pancreata**—Agencies are discussing policies involving pancreas procurement costs.

- **Recommendations for legislation and administrative actions to increase supply of pancreata**—Discussions will help inform agency determinations regarding recommendations for future legislation or administrative actions.

- **Existing mechanisms to collect and coordinate outcomes data from trials**—The Collaborative Islet Transplant Registry (CITR) collects, analyzes, and communicates data on islet transplants performed in North America and five European centers. The CITR is working with UNOS, the Islet Cell Resource Centers, and the Clinical Islet Transplantation Consortium.

- **Implementation of the multiagency clinical investigations of pancreatic islet cell transplantation**—The report provided an update of the CIT trial involving Medicare beneficiaries.

The narrative addressing these seven items included in the 2005 DMICC Annual Report will be updated for the 2006 DMICC Annual Report. Dr. Hanlon asked DMICC representatives to begin thinking about updating relevant sections of the 2005 report. As in the past, the previous years report (i.e., the 2005 report) will be sent to DMICC members in the fall, with a request to provide an update of their IC's or agency's activities for the 2006 report. At the same time, DMICC members will be sent the 2005 narrative on islet transplantation and asked to update it or provide new information, if applicable. NIDDK will consolidate the input and update the narrative for submission in the 2006 DMICC annual report.

ADJOURNMENT

Dr. Fradkin thanked participants for attending and taking part in this important meeting. The meeting was adjourned at 12:40 p.m.