

2007 Scientific Summary of the Collaborative Islet Transplant Registry (CITR)

Background and Purpose. Islets are clusters of insulin-producing cells located in the pancreas. In patients with Type 1 diabetes mellitus (T1DM) all islets are destroyed by an autoimmune attack and patients need to inject insulin every day to stay alive. The total prevalence of diagnosed IDDM in the United States (US) (all ages, 2005) is approximately 1,400,000-2,800,000 people (<http://diabetes.niddk.nih.gov/dm/pubs/statistics>). For patients with T1DM and poor kidney function, a whole pancreas transplant is sometimes performed. For patients with severe hypoglycemia, an alternative experimental procedure uses insulin-producing cells (islets) extracted from a donor pancreas. These are implanted typically via the portal vein in the liver, where the islets produce insulin as needed by the recipient.

To accumulate and compile the data from all completed and ongoing studies between 1999 and present, the National Institute of Diabetes & Digestive & Kidney Diseases funded the Collaborative Islet Transplant Registry (CITR) for data collection from North American programs. The Juvenile Diabetes Foundation has granted additional funding to include the participation of selected European and Australian centers. The mission of CITR is to expedite progress and promote safety in islet/beta cell transplantation through the collection, analysis, and communication of comprehensive and current data on all islet/beta cell transplants. Each year the Registry provides a comprehensive overview of the cumulative data to date since 1999. This fourth report, published in 2007, summarizes information on patients who received one or more islet cell transplants between 1999 and 2006 inclusive. CITR Annual Reports are public and can be downloaded or requested in hard copy at www.citrregistry.org.

In the United States, islet transplantation is an experimental procedure that is regulated by the Food and Drug Administration (FDA). About 45 medical institutions in the US and Canada have been or are currently active in islet transplantation since 1999, or are in the process of starting a program.

This year's report also includes data from one European center whose participation began in 2006. For most of the analyses, this center's data are pooled with the US and Canadian data for the basic descriptions of recipient characteristics, donor, organ and islet characteristics and safety and efficacy outcomes. Descriptions of funding sources and North American transplant activity exclude this European center's data. No center-specific data are presented in any CITR reports.

Most ongoing protocols are experimental in nature and have differed minimally in the entry criteria for patients and in the types of immunosuppression therapy used to prevent rejection of the infused islet cells. It is the goal of these studies to help determine if improvement in the glycemic control and/or reversal of insulin dependency can be achieved, to assess the long-term function of successful islet transplants and risks of associated immunosuppressive medication, and if the natural history of diabetes complications is altered. Each center publishes

the results of their studies and provides information regarding their open and recruiting protocols through their own means and/or at the National Library of Medicine's developed website www.clinicaltrials.gov.

Patients and Methods.

Patients typically eligible for islet transplantation are those who have T1DM for more than five years, are between 18 and 65 years of age, and have very poor diabetes control including severe hypoglycemia. Poor diabetes control can manifest as frequent episodes of critically low blood sugar levels (hypoglycemic episodes and insulin reactions) requiring the assistance of another person, wide swings of blood sugar levels (blood glucose lability), or consistently high HbA_{1c} levels (> 8%).

Data reported to the Registry are abstracted from medical information that is routinely collected by investigators for scientific evaluations and for reports to the multiple agencies and entities required by US Food and Drug Administration (FDA) regulated trials or according to the requirements of the respective nation. In US centers, demographic information is collected in CITR only once, at the time of the islet transplant recipient's registration. For each islet/beta cell infusion, information is collected on the pancreas donor(s), islet processing and testing of all pancreata used for the infusion procedure, and recipient status from screening through the early transplant period.

Follow-up data are abstracted at Day 30, Month 6 and Month 12 post first infusion procedure for four main indicators (severe hypoglycemic episodes, hemoglobin A1C, fasting blood glucose and C-peptide), and daily for insulin status. Detailed follow-up data are abstracted at Month 6, Month 12, and annually post infusion. At each new infusion, a new follow-up schedule is established to abstract data at six-month and annual anniversaries of the last infusion. There is also data abstraction on event-driven data including reportable adverse events, recipient's vital status, non-islet transplant and follow-up, islet graft dysfunction, loss to follow-up, and transfer of the recipient to another islet transplant center. A copy of the CITR data collection forms may be requested from the CITR Coordinating Center (citr@emmes.com), or viewed at the CITR Website (www.citregistry.org).

CITR utilizes The Coordinating Center's (The EMMES Corporation, Rockville, MD) web-based data entry and management systems to capture data on recipients and donors. Donor and islet processing data are also obtained through data sharing agreements with the United Network for Organ Sharing (UNOS) and the Administrative and Bioinformatics Coordinating Center (ABCC) of the Islet Cell Resource Centers (ICR), respectively. Pooled together from all protocols, these data characterize and follow general trends in safety and efficacy for recipients of islet transplantation. Outcomes can be related to recipient characteristics, donor information, islet procurement, processing and product characteristics, transplant techniques, and treatment protocols.

All grade 3, 4 and 5 adverse events, according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute, and all serious adverse events (regardless of grade) are reported to CITR. Respective CITR Principal Investigators currently determine the relationship of the adverse event to the immunosuppression therapy and to the islet infusion procedure at the time adverse event forms are completed.

The registry data exists because of the voluntary participation of the transplanting centers, with written informed consent by the islet recipients. While the CITR Registry likely represents the most comprehensive collection of the human islet transplantation experience since 1999, there may exist uncontrollable biases and imbalances including selective reporting and differences in clinical care and decision-making. Even with the diligent efforts of the participating centers, the total number of cases and outcomes remains relatively small. Hence, the aggregate results should be interpreted cautiously.

The data are continuously reviewed by the CITR Coordinating Center for quality assurance, errors and data outliers. For this report, data queries were identified and the database updated by the islet transplant centers. The database was closed for analysis on April 1, 2007 for data on recipients that were registered in CITR as of December 31, 2006.

The 2007 CITR Annual Report presents descriptive summary information on all islet allograft recipients, procedures, donors and islet preparations included in the database as of the cut-off date, either aggregately or by islet-alone (IA) or islet-after-kidney (IAK) recipients. Descriptive statistics include distribution summary statistics such as mean and standard deviation or standard error, median and interquartile range (IQR), or distributions/bar charts for categorical variables. Box and whisker plots show the mean as a star, median as a central line, the IQR as the box, and $\pm 1.5 \times \text{IQR}$ as the whiskers; outliers beyond the whiskers are plotted as individual points. Extreme outliers may be excluded from the graph to avoid overall distortion but are footnoted.

Primary outcomes are: achievement of insulin independence; maintenance/loss of insulin independence; HbA_{1c} level; severe hypoglycemia; hypoglycemia status; C-peptide level; islet graft dysfunction or loss; and combinations of these. These are analyzed variously as time-to-event (Kaplan-Meier) estimates or frequency distributions of categorical status such as insulin independent, insulin dependent with detectable C-peptide or absence of graft function (three mutually exclusive and exhaustive states). Events are analyzed by post-first infusion censored at re-infusion, complete islet failure or last follow-up (whichever occurs first), and also post last infusion up to last follow-up. Increasing levels of missing data accrue with longer follow-up times. Patients lost to follow-up are imputed to have discontinued their immunosuppression regimen and experience complete islet failure. A small number of patients have no follow-up to determine their status regarding these events, and are excluded from analyses.

Analysis of the effect of various factors on the primary outcomes has begun and will continue as the registry grows and the data are more completely reported. Explanatory factors include pre-infusion recipient, donor, procurement and final product characteristics, as well as time-dependent factors such as re-infusion and the occurrence of other events and subsequent interventions, which present competing risks. Methods to handle the issues of competing risks are being applied to the analyses and include censoring for one event -- such as achievement of insulin independence -- based on the timing of another event such as complete graft loss. Analyses are presented for events occurring after single infusion up to re-infusion, current follow-up or complete graft loss, contrasted to analyses conducted on outcomes after the recipient's last infusion regardless of the total number of infusions the recipient has received.

Secondary endpoints include: measures of primary complications of diabetes such as fasting and stress glucose and C-peptide levels, and HbA_{1c} levels; measures of metabolic function such as the mixed meal test, oral glucose tolerance test, mean amplitude of glycemic excursion (MAGE), and others administered according to local protocols; measures of secondary

complications of diabetes including nephropathy, neuropathy, and retinopathy among others; measures of kidney and liver function, lipid and blood pressure stasis and concomitant medications; and adverse events reporting.

RESULTS

Islet Allograft Transplantation Activity 1999-2006. All 45 North American medical institutions with an identified islet transplant program between 1999 and 2006 responded to a general questionnaire. Thirty-one of the 45 reported performing at least one islet allograft transplant. The remaining 14 programs have not had any open protocols or were in the process of starting their islet allograft transplant program. Exhibit A displays the activity of North American islet transplant centers for 1999-2006, including the total number of recipients and infusions, and according to the centers' participation in CITR.

Exhibit A

North American Islet Allograft Transplant Centers, Recipients and Infusions Total Performed and Total Reported to CITR 1999-2006

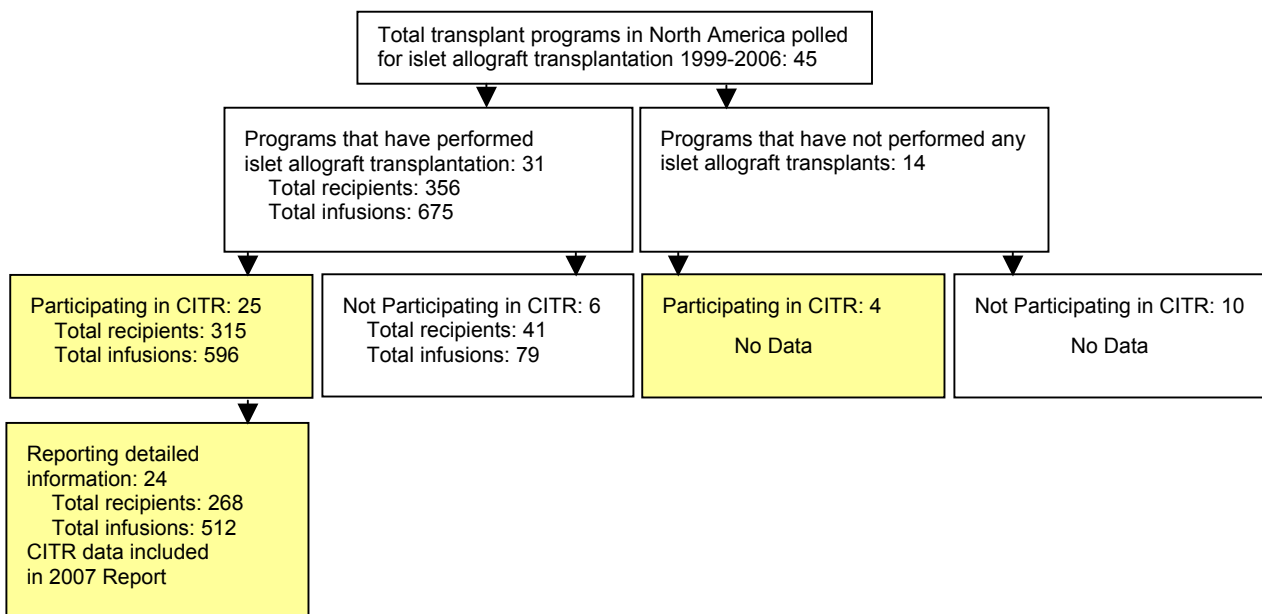
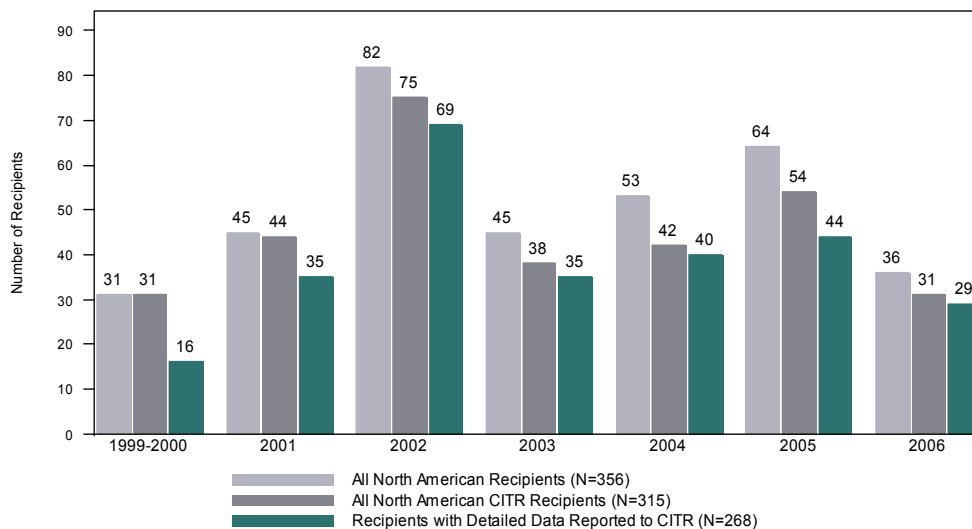


Exhibit B displays the data collected from the 31 active islet transplant programs in North America from 1999 through 2006. To the knowledge of the Registry, this table is inclusive of all human-to-human islet transplant programs in North America.

Exhibit B

Total Number of Islet Transplant Recipients, Recipients at CITR-Participating Centers, and Recipients with Detailed Data Reported to CITR By Year of First Islet Allograft Infusion

All North American Islet Transplant Centers 1999-2006



One European center joined the Registry in 2006, registered all past participants and reported data for inclusion in this report. Pooling the reported data from the North American and European centers, the CITR registry comprises 292 allograft recipients with detailed data reported as of the data cutoff, and 579 infusion procedures derived from a total of 634 donors. Seventy-six of the recipients (26%) received a single islet infusion, 149 (51%) received two, 63 (22%) received three, and four (1%) received a total of four islet infusions. On average, recipients received a total of 819,160 (SD 352,575) total islet equivalents (IEQs), or 12,669 IEQs/kilogram body weight (SD 5,808).

Of the total 292 North American and European recipients included in this report, 262 (90%) were recipients without a previous kidney transplant who received one or more islet-alone infusions (IA), while 30 recipients (10%) had previously received a kidney transplant (IAK).

Recipient Characteristics. The mean age of islet allograft transplant recipients in CITR is 43.7 years (range 19-67) and the mean duration of diabetes is 29 years (range 5 to 53). The mean weight of the participant is 66 kg (range 35 to 98) and the mean body mass index (BMI) is 23.7 kg/m² (range 15 to 37). About 64% of the participants are female. There is limited racial and ethnic diversity among the participants with this data reported.

Approximately 37% of the 292 allograft islet transplant participants were on an insulin pump prior to their first infusion and 98% of the participants were on the pump or were taking three or more insulin injections per day. At baseline, 91% of the participants had a basal C-peptide < 0.5 ng/mL and 81% had a HbA_{1C} > 6.5%. The mean daily insulin requirement of participants prior to their first infusion procedure was 36.9 units (SD 13.6) and the subset on intensive insulin

therapy had received intensive therapy for a mean of 18.7 years (SD 13.1). The mean fasting blood glucose for all participants was 171.6 mg/dL (SD 91.8), mean HbA_{1C} was 7.7% (SD 1.3), and the mean basal C-peptide was 0.1 ng/mL (SD 0.2).

Compared to recipients of a single infusion, recipients of three infusions were taking a higher baseline daily insulin dose, had a higher HbA_{1C} and had a lower PRA percentage.

Donor Information. There were no living donors. The mean age of donors was 43 years (range 8 to 75) and the mean body mass index was 29.1 kg/m² (range 13 to 69). The mean time from cross clamp to pancreas recovery was 38 minutes (SD 22) while the mean cold ischemia time was 7.3 hours (range 1 to 27). Approximately 57% of the donors were male, 13% were Hispanic and 89% were white. Fifty-seven percent of the donors had a cerebrovascular/stroke as cause of death while 29% experienced a head trauma. Approximately 34% of the donors had a history of hypertension and 19% had a history of alcohol dependency.

Thirty-three percent of the donors received a transfusion prior to organ procurement, while only 6% received a transfusion during the organ procurement surgery. Fifty-seven percent of the donors received steroids, 37% of the donors received insulin and 97% received at least one vasopressor during the donor's terminal hospitalization. There was a report of one donor testing positive for Anti HBC and this donor was used for a hepatitis B immunized recipient. The mean serum creatinine of the donors was 1.2 mg/dL.

Pancreas Procurement. In 64% of the pancreas procurement procedures, the pancreas procurement team was not related/affiliated with the processing/transplant team, while 91% of the processing procedures took place at the same institution as the islet transplant center. The median duration of cold ischemia was 7 hours (range 1 to 27). UW, Two Layer (UW + PFC, UW + HTK, or SCOT + PFC), and UW followed by Two Layer were the most common methods used for pancreas preservation.

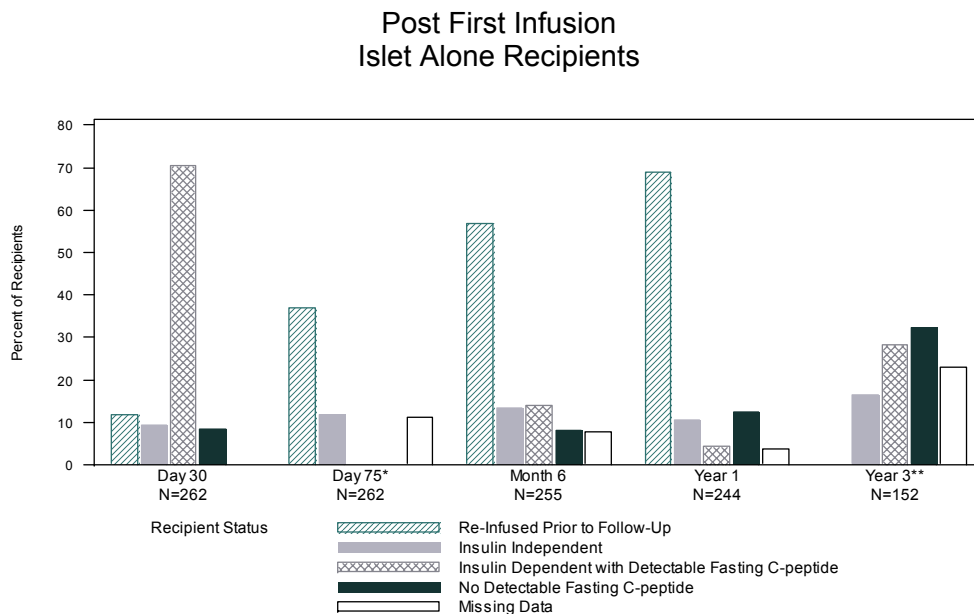
Liberase HI was the collagenase type used during most islet processing (94%) followed by Thermolysin/Liberase combinations (4%). All of the pancreata processed used a density gradient for islet purification. When cultured, defined as six or more hours in a specially prepared nutrient medium, the mean culture time was 30.7 hours (range 6.0 to 96.0). Of the 634 islet preparations reported to CITR, nine final preparations showed a positive aerobic culture, five showed a positive anaerobic culture, eleven showed a positive fungal culture, and one tested positive for mycoplasma.

Islet final product characteristics were related to recovery time, cold ischemic time, donor body mass index, and donor age by Spearman rank correlation (data not shown). These relationships deserve more in-depth analysis, especially in correcting correlated factors to outcomes.

Immunosuppression Therapy. The majority (60%) of the islet transplant alone recipients at the time of first infusion were on a Daclizumab, Sirolimus, and Tacrolimus only immunosuppression regimen. Daclizumab was used for induction alone in 74% of IA first infusions, and in combination with other T-cell antibodies in another 6% of first infusions. Antithymocyte globulin was given alone or in combination in 11% of first infusions.

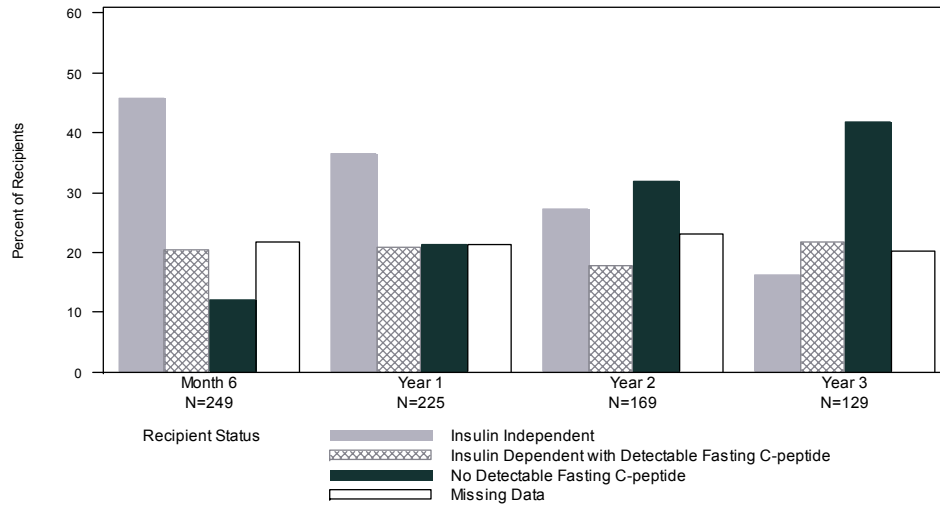
Graft Function. After the first infusion, increasing proportions of islet-alone recipients are re-infused: 12% by Day 30, 37% by Day 75, 57% by Month 6, and 69% by Year 1 (Exhibit C-1). The proportion that is insulin independent without re-infusion remains fairly constant at 9-13% throughout the first year. An additional 4-14% of all IA recipients retain detectable C-peptide over the first year with insulin dependence but without re-infusion. Of all 262 IA recipients, 58% are expected at three-years post first infusion, at which time, regardless of the total number of infusions received, about 16% are insulin independent, 28% are insulin dependent with detectable C-peptide, 32% have no detectable C-peptide or lost to follow-up, and 23% have missing data (required but not yet reported). Analyzed from last infusion (Exhibit C-2), where re-infusion is not an issue, the percentage of all IA recipients that is insulin independent declines steadily from 46% at Month 6 to 16% at Year 3. The proportion with loss of islet function (reported graft failure or no detectable C-peptide or lost to follow-up with imputed graft failure) increases steadily from 13% at Month 6 to 42% at Year 3. A stable 18-22% retains graft function with exogenous insulin over the three years; every time point has 20-23% missing data. These trends of increasing prevalence of graft loss and decreasing prevalence of insulin independence over time post last infusion prevail regardless of the total number of infusions given, although the rates differ somewhat among the three groups (data not shown).

**Exhibit C-1
Prevalence of Insulin Status and Detectable Fasting C-Peptide**



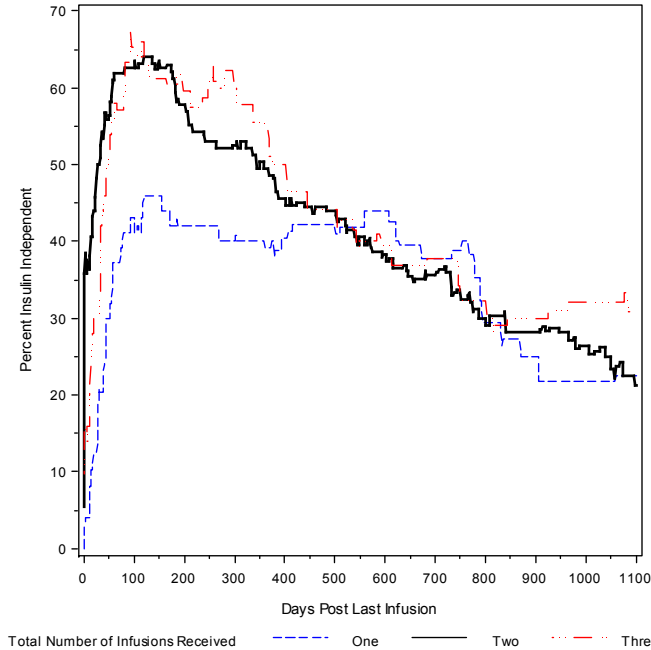
**Exhibit C-2
Prevalence of Insulin Status and Detectable Fasting C-Peptide**

Post Last Infusion
Islet Alone Recipients



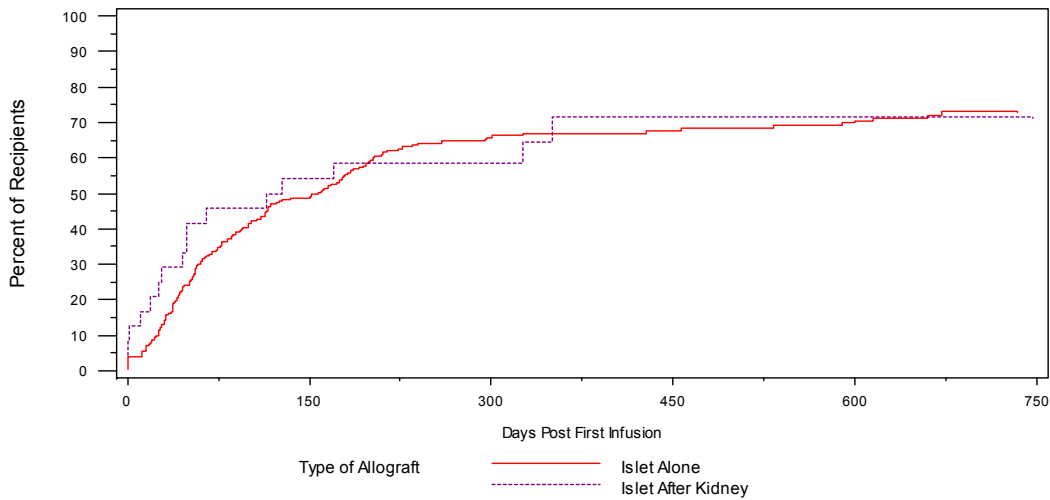
Focusing only on the insulin independence status (available daily with about 20% missing data on any day), the prevalence of insulin independence from last infusion declines from about 60% at Month 4 to about 24% at Year 3 (1100 days) post last infusion (Exhibit D). Two or three infusions boost the prevalence of insulin independence in the first year to a peak of about 64%, with a subsequent decline to levels that are comparable to those with a single infusion.

Exhibit D
Prevalence of Insulin Independence Post Last Infusion
By Total Number of Infusions Received
Islet Alone Recipients



As incidence or cumulative rates of ever achieving insulin independence after islet transplantation, 67% of the IA and IAK recipients combined achieve insulin independence in the first year post first infusion (not censored at re-infusion or graft loss), and by Year 2 this increases to 73% (Exhibit E).

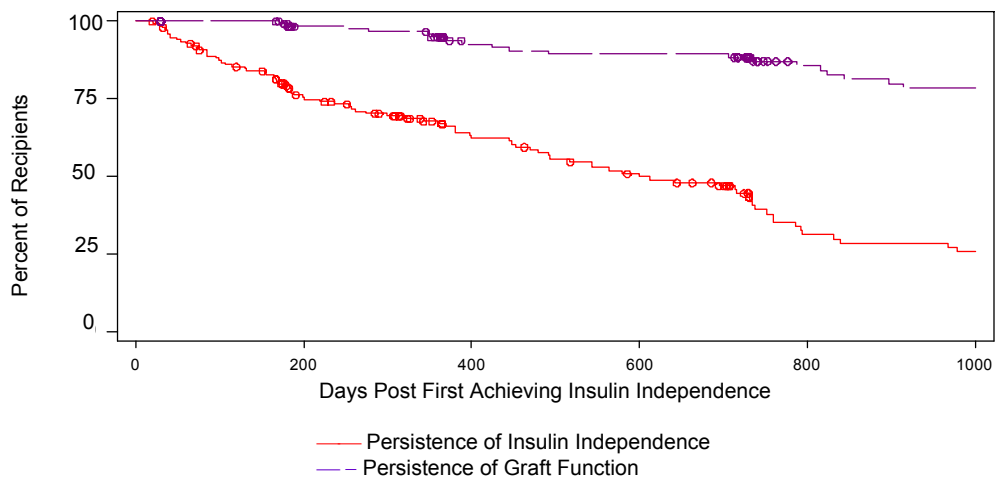
Exhibit E
Achievement of Insulin Independence After Islet Transplantation
Not Censored at Re-Infusion or Graft Loss



Stratified by the number of infusions per recipient, the greater the number of infusions, the higher the rate of achieving insulin independence (data not shown). However, the proportion of recipients attaining insulin independence quickly post each re-infusion is quite higher for second infusion and slightly higher post third infusion than for first infusion.

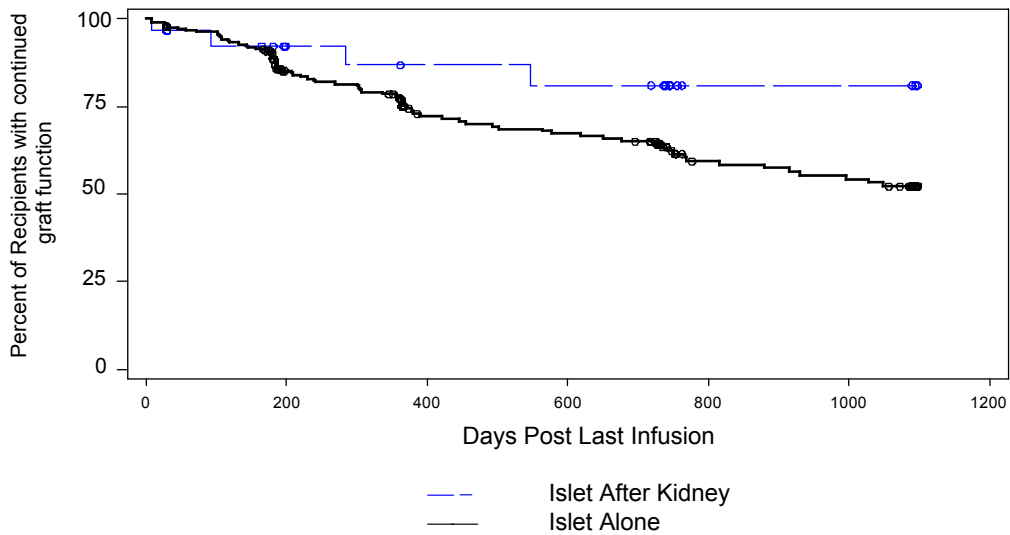
Over time there is a decrease in the sustainability of insulin independence (Exhibit F). For all participants who ever achieved insulin independence, only 67% have retained this status one year after achieving it and this decreases to 45% at two years. Three infusions increase the likelihood of retaining insulin independence.

Exhibit F
Persistence of Insulin Independence and Persistence of Graft Function
Islet Alone Recipients Achieving Insulin Independence
Not Censored at Re-Infusion



Similarly, graft function is lost over time. Viewed as Kaplan-Meier estimates (Exhibit G), only 52% of IA recipients retained function by Year 3 post last infusion. Long-term graft function is more likely in recipients who achieve insulin independence at any time during their one to several islet infusions (data not shown).

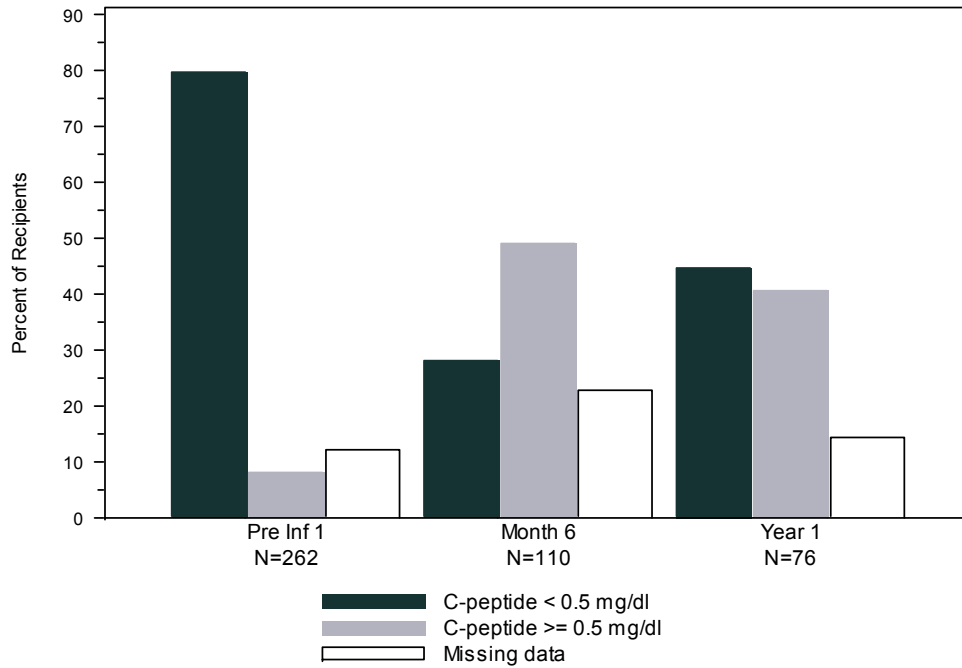
Exhibit G
Persistence of Islet Graft Function (IA, IAK)



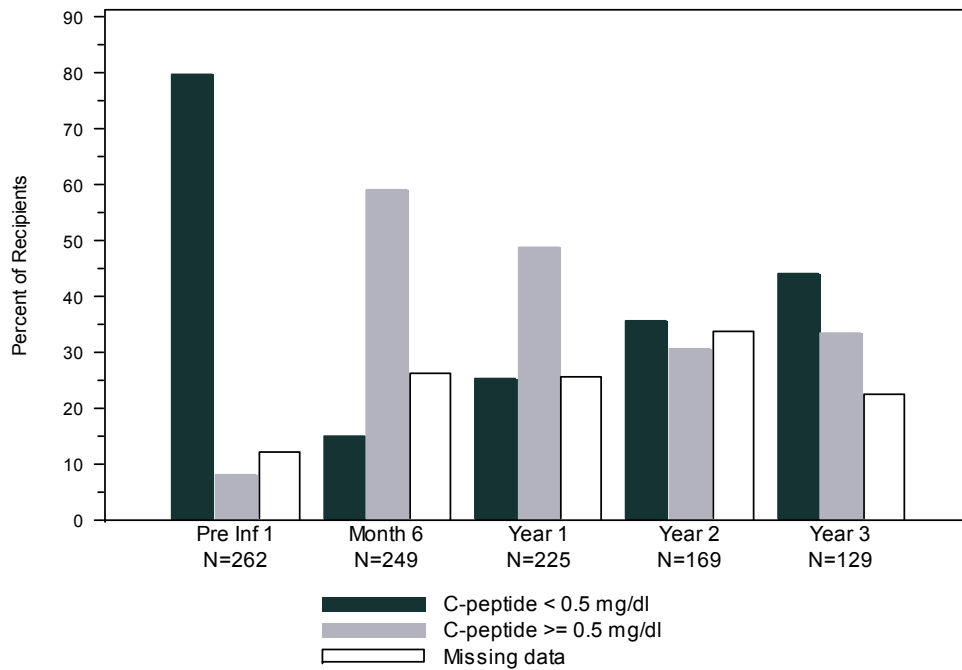
C-peptide levels are substantially increased by islet transplantation. The percent of IA recipients with C-peptide >0.5 ng/mL increases from 8% pre-infusion to 49% at Month 6 and 41% at Year 1 post first infusion (censored at re-infusion, Exhibit H, top), with 33% retaining this level of function at Year 3 post last infusion (Exhibit H, bottom).

Exhibit H
C-peptide \geq 0.5 ng/mL

Post First Infusion



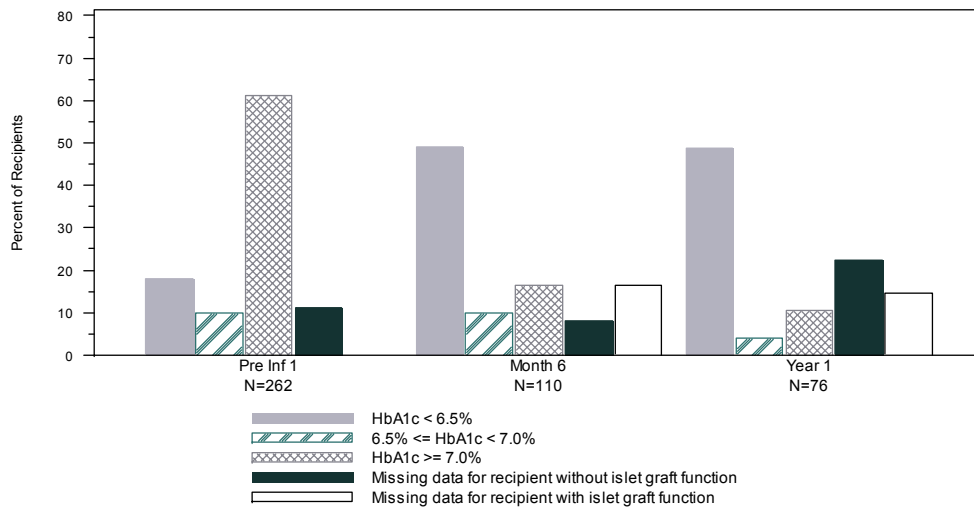
Post Last Infusion



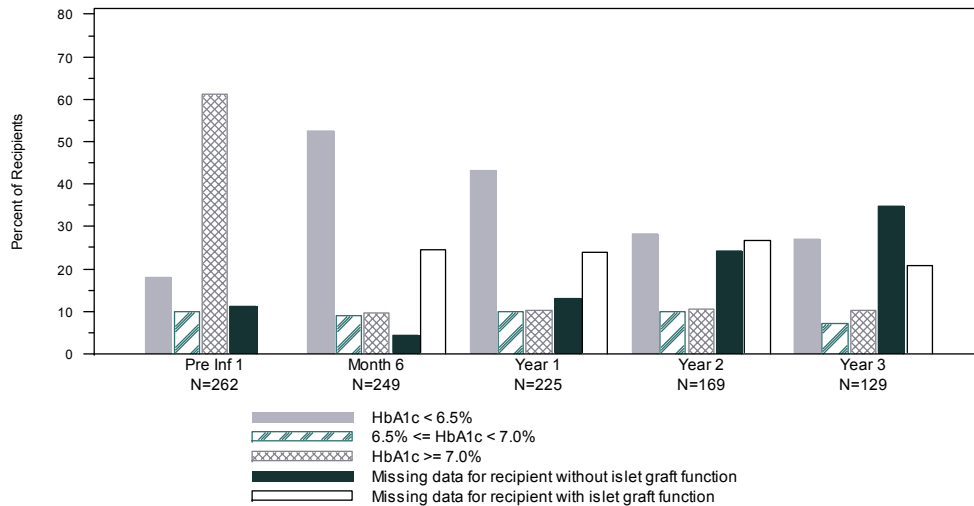
HbA_{1c}. HbA_{1c} levels are improved substantially by islet transplantation. The percent of IA recipients with HbA_{1c} < 7.0% increases from 28% pre-infusion to 59-75% at Month 6 and 53-67% at Year 1 post first infusion, censored at re-infusion (Exhibit I). In these percentile ranges, the lower estimate represents the case where all missing data are counted as HbA_{1c} ≥ 7.0% whereas the upper estimate assumes all missing data for recipients with graft function have HbA_{1c} levels < 7.0%. Post last infusion, these rates are 61-86% at Month 6 and 34-55% at Year 3. Notably, the percent with measured values ≥ 7% remains fairly constant at about 10% throughout follow-up.

Exhibit I HbA_{1c}

Post First Infusion



Post Last Infusion



Severe Hypoglycemic Events.

There continues to be a striking decrease in the prevalence of severe hypoglycemic events that occur both post first and post last infusion procedure. Severe hypoglycemia prevalence is reduced from 76-87% pre-infusion to less than 5-20% throughout the first year post last infusion, and to 9-43% at three years post last infusion (Exhibit J). In these percentile ranges, the lower estimate represents the case where all missing data are recipients who do not experience severe hypoglycemic episodes whereas the upper estimate assumes all missing data for recipients without graft function are recipients who do experience severe hypoglycemic episodes. Hypoglycemia awareness is also markedly improved and is eroded only by loss of graft function or loss to follow-up (Exhibit K). All participants that experienced a severe hypoglycemic event during follow-up were on insulin at the time of the event.

Exhibit J Severe Hypoglycemia Islet Alone Recipients

Post Last Infusion

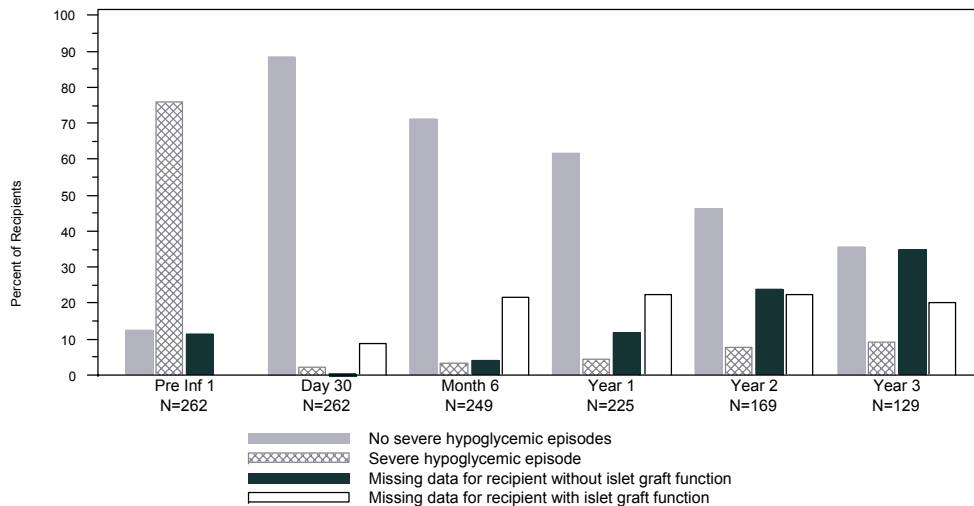
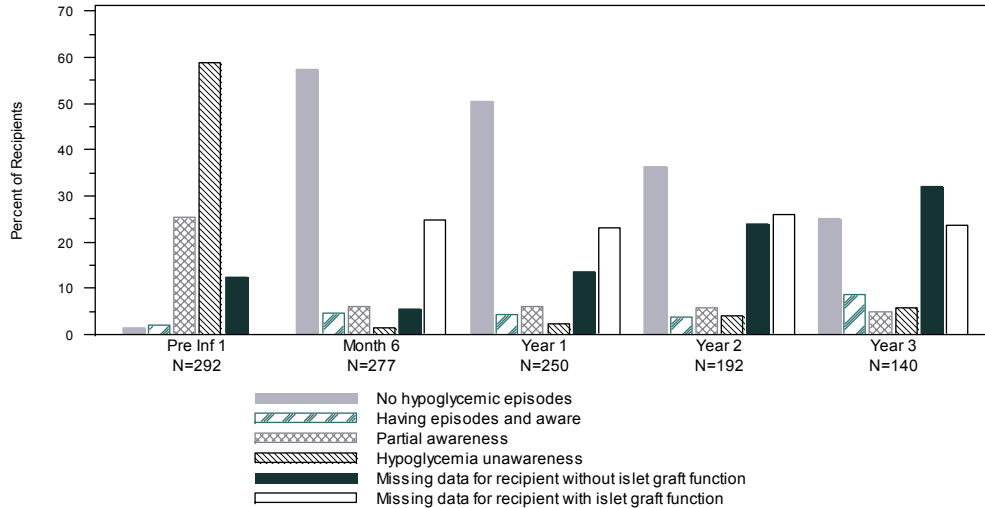


Exhibit K Hypoglycemia Status All Allograft Recipients

Post Last Infusion



Multivariate Cox regression models were used to investigate the effect of pre-infusion factors on primary outcomes of islet transplantation post last infusion. Hazard ratios (HR) less than one indicate a lower risk of the event with higher levels of the factor. Binary factors are coded 0=absent and 1=present. Factors associated with achieving insulin independence included lower HbA_{1C}, insulin not given on Day 0 of infusion (which is likely related to the recipient's recent or current insulin status at the time of infusion), the donor not having been given insulin in hospital, and the total islet equivalents infused (Exhibit L-1).

Exhibit L-1

Multivariate Cox regression: <u>Insulin Independence Post Last Infusion</u>		
Censored at Complete Islet Failure or Last Follow-Up		
(103 events / 170 recipients with data on covariates)		
	HR	p
Baseline HbA1c (%)	0.784	0.002
Insulin Day 0 Last Infusion	0.540	0.003
Donor insulin in-hospital	0.693	0.07
Total IEs/kg received over all infusions	1.039	0.01

Factors protective against complete islet failure include more infusions given, higher age and/or longer diabetes duration, higher stimulation index of the graft(s), and etanercept given at induction (Exhibit L-2).

Exhibit L-2

Multivariate Cox regression: <u>Complete Islet Failure Post Last Infusion</u> Censored at Last Follow-Up (64 events / 204 recipients with data on covariates)		
	HR	p
Total number of infusions received	0.537	0.003
Diabetes duration (years)	0.964	0.03
Age at baseline (years)	0.952	0.01
Mean stimulation index	0.812	0.002
Etanercept at any infusion	0.195	0.006

These multivariate results are preliminary and will require validation with accruing data.

Metabolic Measures.

The choice of which metabolic tests to perform varies from center to center.

Overall, fasting plasma glucose values and HbA_{1C} substantially decrease over time, while basal C-peptide values substantially increase. This trend is seen both overall and by total number of infusions. These results are affected by the recipients' transient insulin status and whether or not they ever achieved insulin independence

Concomitant Medications. Prior to the first infusion, 40% of the recipients were on at least one anti-hypertensive medication and 31% were on a lipid lowering medication. By Year 1 post last infusion, these rates increased to 48% and 61%, respectively.

Elevated Laboratory Tests. Reports of two times or greater than the upper limit of normal (ULN) at any of the specified follow-up time points were minimal for ALT (4%), AST (4%), alkaline phosphatase (6%) and for total bilirubin (1%). There were no reports at this level for total cholesterol and 9 reports (4.5%) for triglycerides. There were 28 reports (13%), of a participant with an increase in their serum creatinine of greater than 0.5 mg/dL above their baseline level.

Adverse Events.

Sixty-five percent of the islet alone recipients experienced at least one adverse event in Year 1; while 41% experienced one or more serious adverse events in this same period. Of the 574 adverse events reported in Year 1 post first infusion for islet alone recipients, 32.5% were related to the immunosuppression therapy and 28.4% were related to the infusion procedure. Of the 211 serious adverse events reported in Year 1 post first infusion for islet alone recipients, 26.5% were related to the immunosuppression therapy and 45.5% were related to the islet infusion procedure. Overall, a total of 337 serious adverse events were reported to the Registry as of datafile closure, with 40.4% of them classified as life threatening and 46% requiring an

inpatient hospitalization. Seventy percent (236 of 337) of serious adverse events occurred in the first year following the participants' first infusion procedure. Over 32% of the serious adverse events were classified by the reporting CITR investigator as related to the islet infusion procedure and 25% related to the immunosuppression therapy. Adverse event relationships to the infusion procedure and immunosuppression regimen are determined by the local CITR Investigator and do not necessarily represent scientific truth. Approximately 91% of the serious adverse events resolved with no residual effects. Most of the reported serious adverse events were categorized as investigations (22%), gastrointestinal disorders (19%) and blood and lymphatic system disorders (15%) as classified by the MedDRA classifications system.

Neoplasms have been diagnosed in ten allograft recipients over the reported period of follow-up (1999-2006):

- four cases of squamous cell carcinoma, three of which were treated and resolved without residual effects and without discontinuation of immunosuppression, and one with no further information;
- one case of basal cell carcinoma, treated and resolved with no residual effects, occurring after discontinuation of immunosuppression for islet graft failure;
- one case of ovarian mucinous cystadenoma, diagnosed the day after first infusion, treated and resolved with no residual effects;
- one case of breast cancer first diagnosed 22 months post first infusion, treated, with immunosuppression continued; one month later, metastatic carcinoma of lymph nodes was identified and treated; immunosuppression was discontinued.
- one case of papillary thyroid cancer at 21 months post first infusion, treated and immunosuppression continued;
- one case of pulmonary nodules, treated but persistent; further follow-up is pending;
- one case of papillary carcinoma, diagnosed two months post first infusion; treated and resolved without sequelae; previous history of thyroid adenoma.

Reported Deaths. There have been four reports of death to the Registry; a viral meningitis attributed death occurring more than three years following the person's second islet infusion, a drug toxicity (acute methadone and diphenhydramine) 70 days post the person's third infusion, a stroke more than two years post the person's second infusion and a death due to unknown causes (discovered in obituaries) more than four years post the person's second infusion.

Conclusions. Islet transplantation continues to show short-term benefits of insulin independence, normal or near normal HbA_{1C} levels, and sustained marked decrease in hypoglycemic episodes. Long-term primary efficacy of safety of immunosuppression as well as effects on secondary complications are less well understood and are the focus of ongoing research. The Registry is growing large enough to begin investigating factors predictive of and/or associated with primary outcomes.

The Collaborative Islet Transplant Registry (CITR) is sponsored by the National Institute of Diabetes & Digestive & Kidney Diseases under contract number N01-DK-1-2472 to The EMMES Corporation. Reprints and additional information may be requested via email to citr@emmes.com or through the CITR website at www.citrregistry.org.

