



2008 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 insulin dependent diabetes mellitus (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>). In patients with T1DM and poor kidney function, a whole pancreas transplant is sometimes performed. T1DM patients with severe hypoglycemia may be eligible for an alternative procedure using insulin-producing cells (islets of Langerhans) extracted from a deceased donor pancreas which, in the US, is an experimental procedure. A small subset of these allogenic islet recipients have previously received a kidney transplant for end-stage renal disease and were already receiving long-term immunosuppression therapy at the time of their islet transplant. Yet another group of islet recipients are those whose own islets are reinfused after removal of their pancreas due to a medical indication. These autologous recipients are summarized in a supplemental report. For all three types of recipients, islets 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 the 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 Research Foundation (JDRF) 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 fifth report, published in 2008, summarizes information on patients who received one or more islet cell transplants between 1999 and 2007 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). Thirty-one medical institutions in the US and Canada are currently or were previously active in islet transplantation since 1999.

Detailed data are included from two JDRF-sponsored European centers whose participation began in 2006 and 2007. For most of the analyses, these European 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 European data. No center-specific data are presented in any CITR reports.

Individual transplant units initiate their own independent research protocols to advance the field of islet transplantation. 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 (severe 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 and long-term 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 Terminology Criteria for Adverse Events (TCAE) of the Clinical Islet Transplantation Consortium (CIT), 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 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, 2008 for data on recipients that were registered in CITR as of December 31, 2007.

The 2008 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. A small number of patients have no follow-up to determine their status regarding these events. They are accounted for but may be excluded from selected 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.

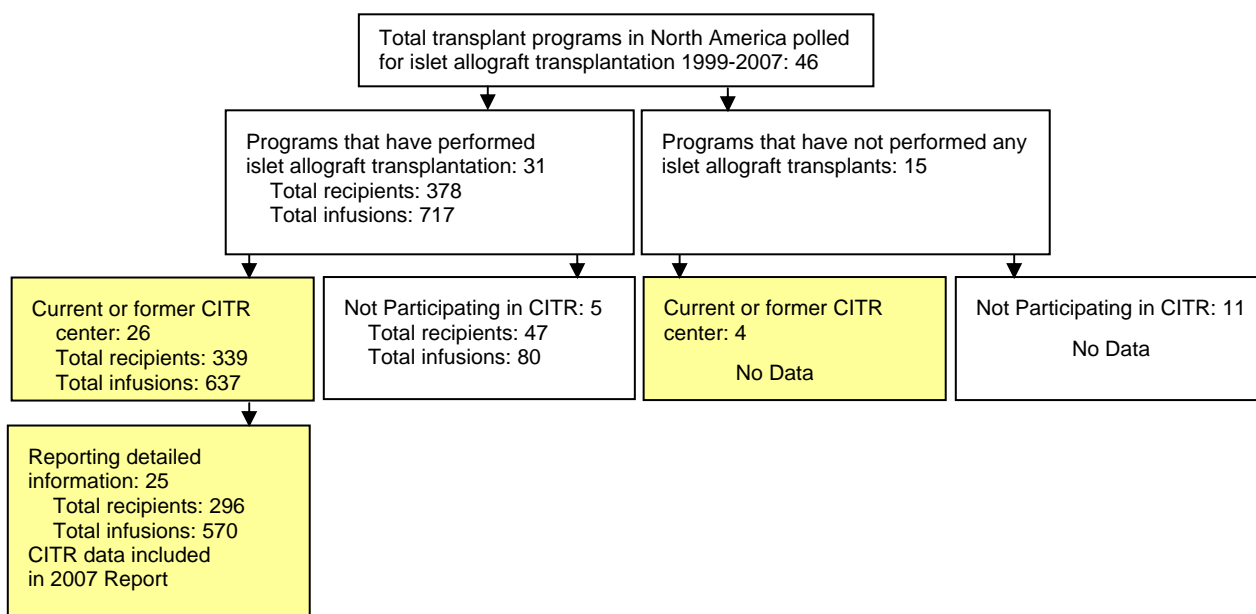
Secondary endpoints include: measures of primary complications of diabetes such as fasting and stress glucose and C-peptide levels, and HbA_{1C} levels; measures of metabolic function such as the mixed meal test, oral glucose tolerance test, mean amplitude of glycemic excursion (MAGE), and others administered 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 1999-2007. All 46 North American medical institutions with an identified islet transplant program between 1999 and 2007 responded to a general questionnaire. Thirty-one of the 46 reported performing at least one islet allograft transplant. Exhibit A displays the activity of North American islet transplant centers for 1999-2007, including the total number of recipients and infusions, and according to the centers' participation in CTR.

Exhibit A

North American Islet Allograft Transplant Centers, Recipients and Infusions Total Performed and Total Reported to CTR 1999-2007



Exhibits B1 and B2 display the data collected from the 31 active islet transplant programs in North America from 1999 through 2007. To the knowledge of the Registry, this table is inclusive of all human-to-human islet transplant programs in North America.

Exhibit B-1

**Number of Islet Transplantation Centers Performing Islet Allografts per Year and Number with Data Entered in CITR Database
All North American Islet Transplant Centers 1999-2007**

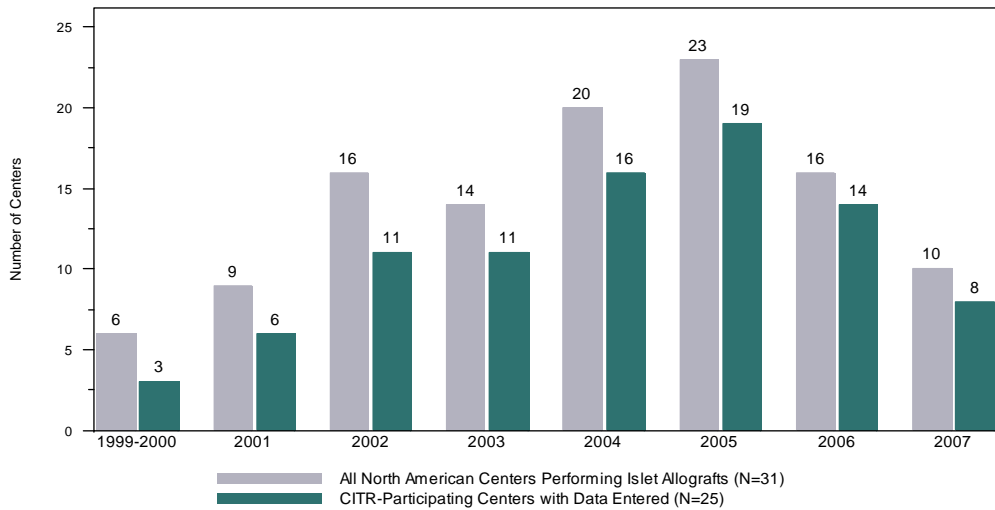
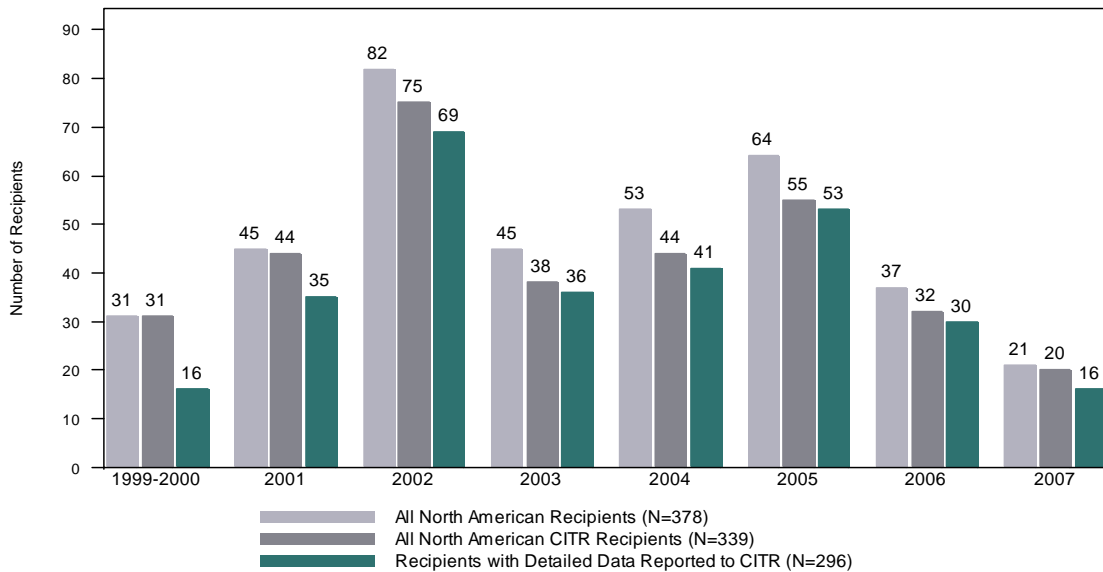


Exhibit B-2

**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 1999-2007**



Two European centers joined the Registry in 2006 and 2007 and contributed data for this report. Pooling the reported data from the North American and European centers, the Registry comprises 325 allograft recipients with detailed data reported as of the data cut-

off, and 649 infusion procedures derived from a total of 712 donors. Eighty-four of the recipients (26%) received a single islet infusion, 164 (50%) received two, 71 (22%) received three, and six (2%) received a total of four islet infusions. On average, recipients received a total of 837,308 (SD 377,481) total islet equivalents (IEQs), or 12,942 IEQs/kilogram body weight (SD 5,974).

Of the total 325 North American and European recipients included in this report, 279 (86%) were recipients without a previous kidney transplant who received one or more islet-alone infusions (IA), while 46 recipients (14%) had previously received a kidney transplant (IAK).

Recipient Characteristics. The mean age of islet allograft transplant recipients in CITR is 44 Years (range 19 to 67) and the mean duration of diabetes is 29 Years (range 2 to 54). The mean weight of the participant is 66 kg (range 35 to 98) and the mean body mass index (BMI) is 23.6 kg/m² (range 15 to 32). About 65% of the participants are female. There is limited racial and ethnic diversity among the participants with this data reported.

Approximately 36% of the 325 allograft islet transplant participants were on an insulin pump prior to their first infusion and 97% of the participants were on the pump or were taking three or more insulin injections per day. At baseline, 92% of the participants had a basal C-peptide <0.5 ng/mL and 83% had a HbA_{1C} >6.5%. The mean daily insulin requirement of participants prior to their first infusion procedure was 37 units (SD 13.5) and the subset on intensive insulin therapy had received intensive therapy for a mean of 16.3 Years (SD 14.0). The mean fasting blood glucose for all participants was 174 mg/dL (SD 93), 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 younger, on the waitlist for less time, 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 1 to 75) and the mean body mass index was 29 kg/m² (range 3 to 69). The mean time from cross clamp to pancreas recovery was 39 minutes (SD 20) while the mean cold ischemia time was 7.3 hours (range 1 to 27). Approximately 59% of the donors were male, 11% were Hispanic and 89% were white. Fifty-five percent of the donors had a cerebrovascular/stroke as cause of death while 31% experienced a head trauma. Approximately 34% of the donors had a history of hypertension and 20% had a history of alcohol dependency.

Thirty-three percent of the donors received a transfusion during hospitalization, while only 6% received a transfusion intraoperatively. Sixty percent of the donors received steroids, 39% of the donors received insulin and 96% 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. Another donor tested positive for RPR-VDRL. 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 90% 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 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 (86%) followed by Blendzyme (7%) and NB1 (6%). 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 26 hours (range 6 to 96). Of the 712 islet preparations reported to CITR, thirteen final preparations showed a positive aerobic culture, six showed a positive anaerobic culture, five showed a positive fungal culture, and one tested positive for mycoplasma.

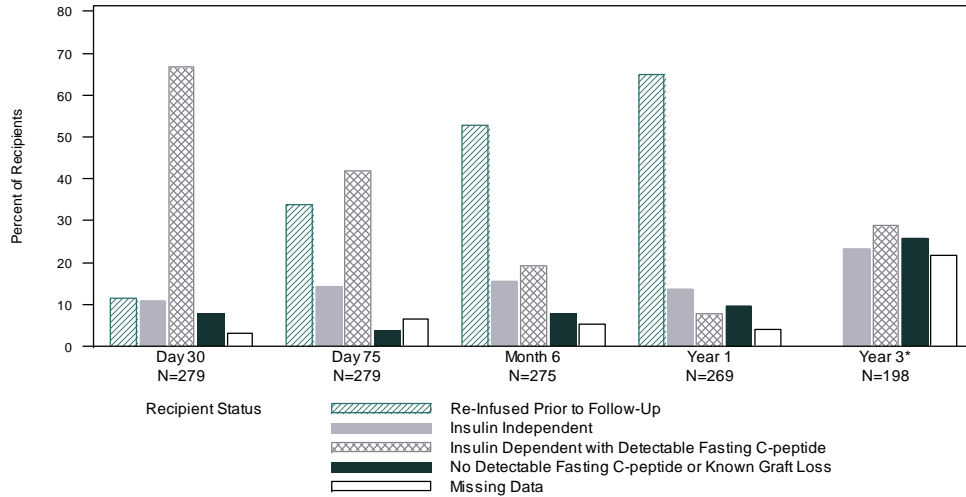
Immunosuppression Therapy. The majority (59%) of the islet transplant alone recipients at the time of first infusion were on a Daclizumab, Sirolimus, and Tacrolimus only immunosuppression regimen. Daclizumab was used for induction alone in 65% of IA first infusions, and in combination with other antibodies in another 12% of first infusions. Anti-thymocyte globulin was given alone or in combination in 12% of first infusions.

Graft Function. After the first infusion, increasing proportions of islet-alone recipients are re-infused: 11% by Day 30, 34% by Day 75, 53% by Month 6, and 65% by Year 1 (Exhibit C-1). The proportion that is insulin independent without re-infusion remains fairly constant at 10-15% throughout the first year. An additional 8-12% of all IA recipients retain detectable C-peptide over the first year with insulin dependence but without re-infusion. Of all 279 IA recipients, 71% are expected at three years post first infusion, at which time, regardless of the total number of infusions received, about 23% are insulin independent, 29% are insulin dependent with detectable C-peptide, 26% have no detectable C-peptide, and 22% 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 are insulin independent declines steadily from 54% at Month 6 to 22% at Year 3. The proportion with loss of islet function (reported graft failure or no detectable C-peptide) increases steadily from 10% at Month 6 to 34% at Year 3. A stable 23-26% retains graft function with exogenous insulin over the three years; the percentage of missing data increases over time. 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

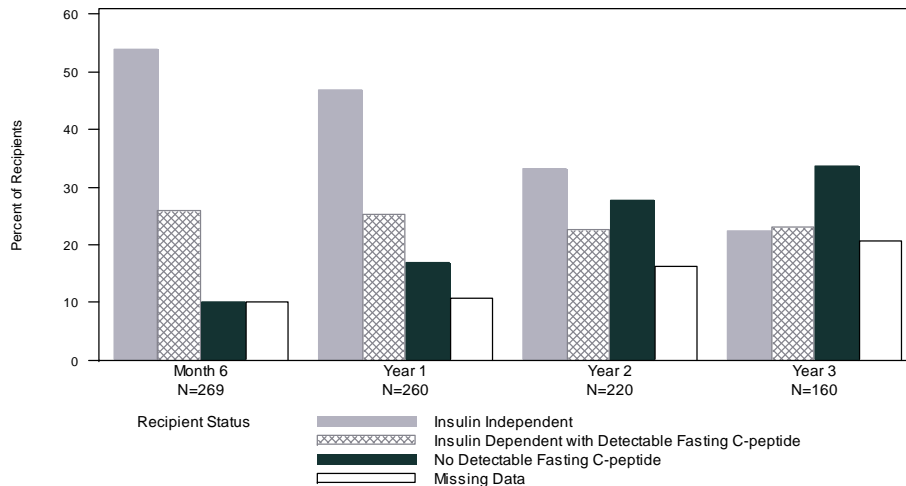
Post First Infusion Islet Alone Recipients



*Year 3 status regardless of re-infusion

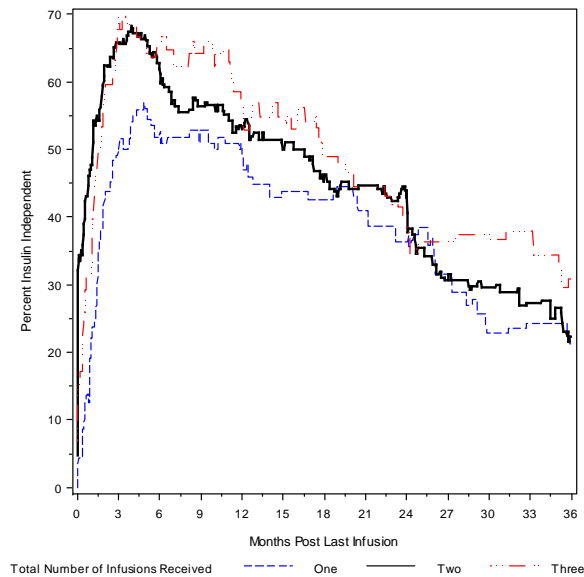
Exhibit C-2 Prevalence of Insulin Status and Detectable Fasting C-Peptide

Post Last Infusion Islet Alone Recipients



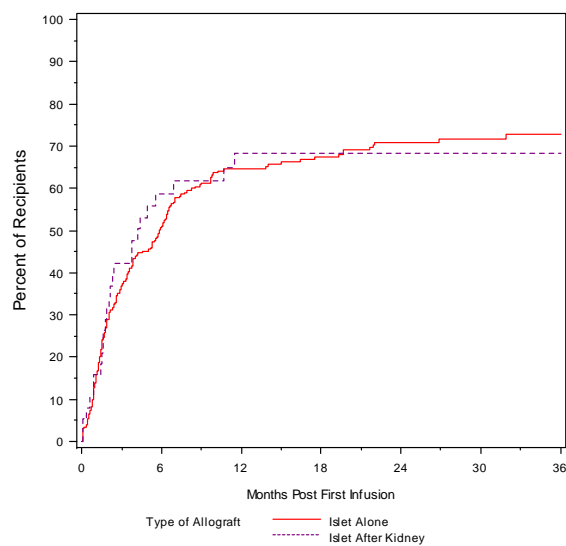
Focusing only on the insulin independence status (available from daily diaries with increasing missing data over time), the prevalence of insulin independence from last infusion declines from 65% at Month 4 to about 24% at Year 3 post last infusion (Exhibit D). Two or three infusions boost the prevalence of insulin independence in the first year to a peak of about 69%, 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, 64% of the IA and IAK recipients combined to 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 70% (Exhibit E).

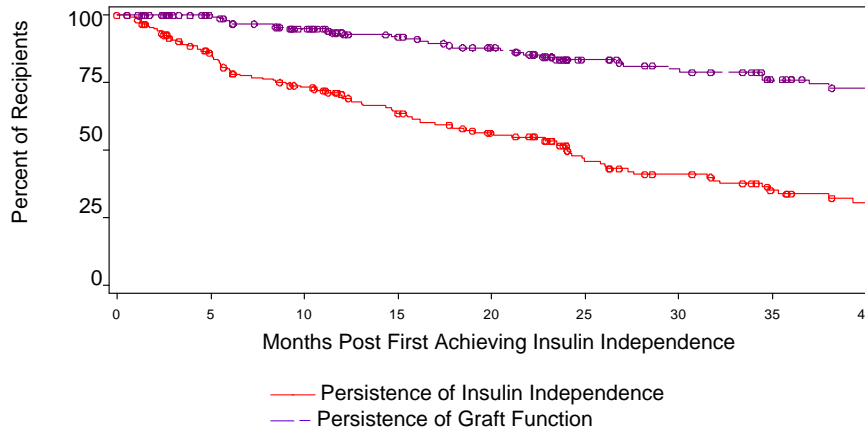
Exhibit E
Achievement of Insulin Independence After Islet Transplantation
Not Censored at Re-Infusion or Graft Loss



The proportion of recipients attaining insulin independence quickly post each re-infusion is much higher for second and third infusion than for first infusion (data not shown).

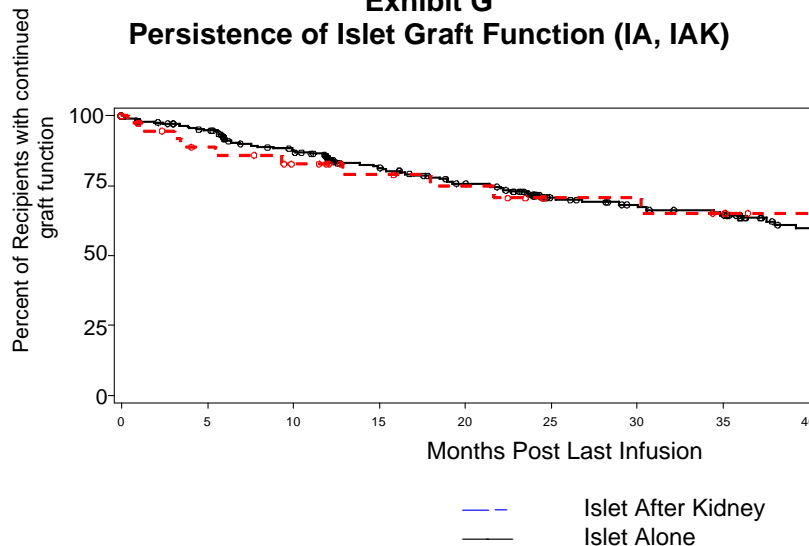
Over time there is a decrease in the sustainability of insulin independence (Exhibit F). For islet alone participants who ever achieved insulin independence, 71% have retained this status one year after achieving it and this decreases to 52% at two years.

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 survival estimates (Exhibit G), 64% 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 some 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 47% at Month 6 and 43% at Year 1 post first infusion (censored at re-infusion, Exhibit H-1), with 32% retaining this level of function at Year 3 post last infusion (Exhibit H-2).

Exhibit H-1
C-peptide \geq 0.5 ng/mL

Post First Infusion

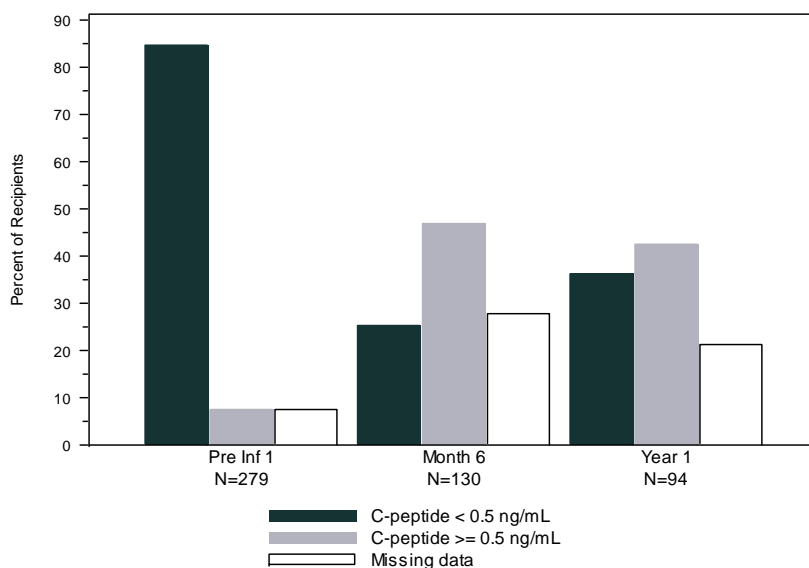
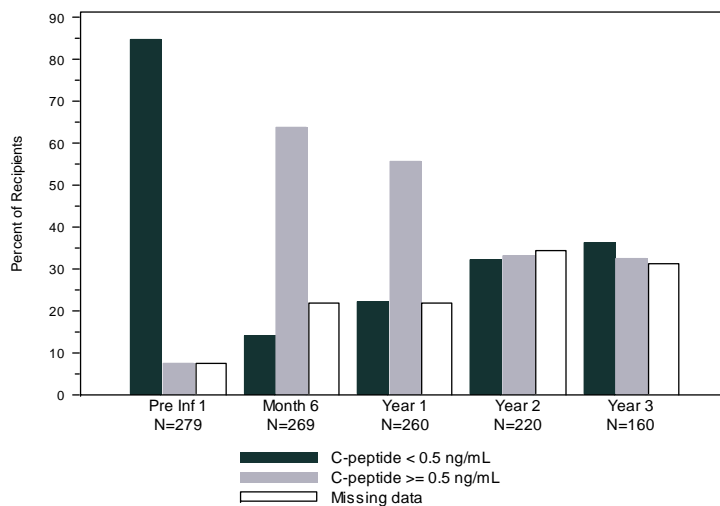


Exhibit H-2
C-peptide \geq 0.5 ng/mL

Post Last Infusion



Severe Hypoglycemia and HbA_{1c}. The prevalence of severe hypoglycemic events decreases dramatically following islet transplantation. Islet transplants also substantially improve HbA_{1c} levels. Taken as a composite outcome (Exhibit I), the percent of IA recipients with HbA_{1c} <6.5% and absence of severe hypoglycemic episodes increases from 2% pre-infusion to 47-69% at Year 1 post last infusion. In this range, the lower estimate represents the case where all missing data are counted as not achieving the outcome whereas the upper estimate assumes all missing data for recipients with confirmed or unknown graft function do achieve the outcome. All participants that experienced a severe hypoglycemic event during follow-up were on exogenous insulin at

the time of the event. Hypoglycemia awareness is also markedly improved and is eroded only by loss of graft function or loss to follow-up (Exhibit J).

Exhibit I Composite Outcome (Hypoglycemia and HbA_{1c}) Post Last Infusion Islet Alone Recipients

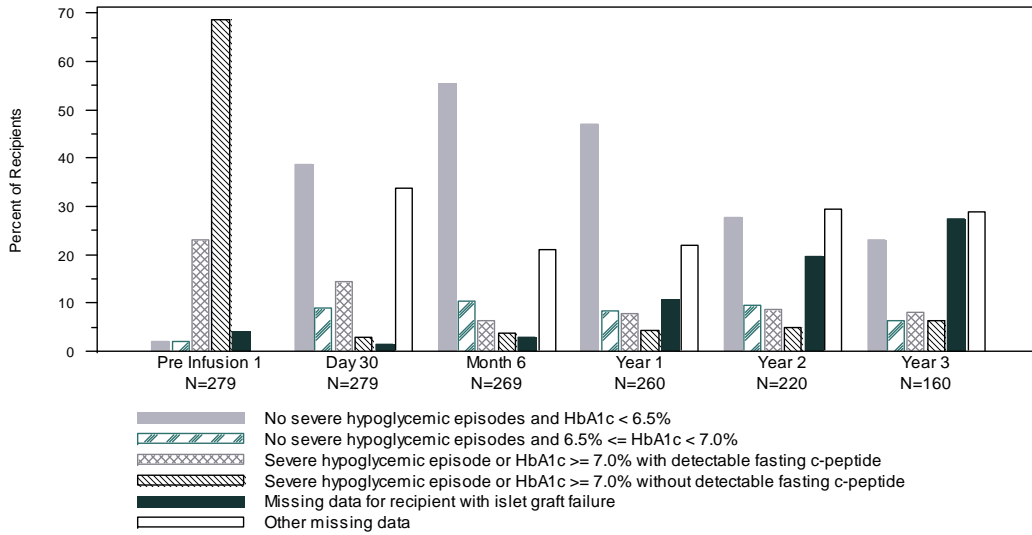
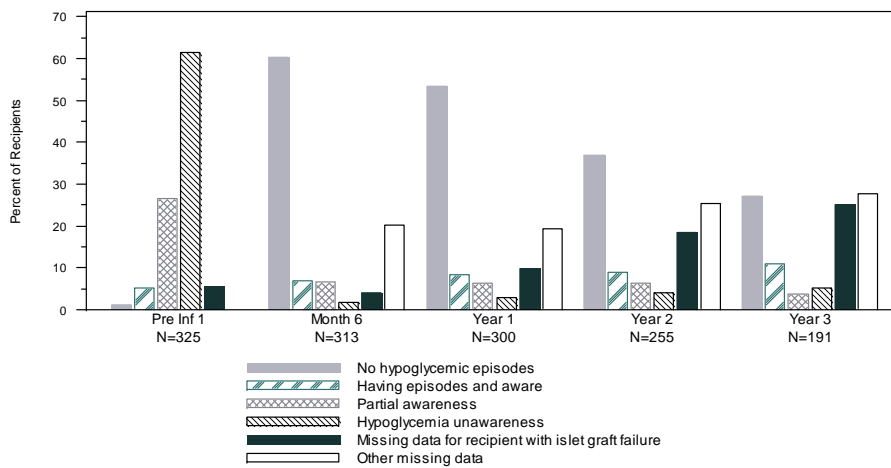


Exhibit J Hypoglycemia Status All Allograft Recipients

Post Last Infusion



Factors of Primary Outcomes. Multivariate Cox regression models were used to investigate the effect of pre-infusion and cumulative 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.

The final multivariate model for insulin independence post last infusion is:

Variable	HR	p
Baseline HbA _{1c} (%)	0.878	0.0541
Donor(s) Hispanic (0=N 1=Y)	0.543	0.0444
Processing/infusion center (0-Unrelated 1-Related)	4.074	0.0058
Islet size (0-small 1-large)	1.719	0.0031
Daclizumab (0-N 1-Y)	1.951	0.0183

Baseline HbA_{1c} is substantially correlated with baseline weight, baseline BMI, baseline daily insulin, fasting glucose, and number of daily injections. Any of these measures of initial control suffices to explain its influence on achieving insulin independence: the better the control, the more likely to achieve insulin independence. Larger islet size (estimated by IEQs/total particles at time of islet counting, here cumulated over all infusions) favors achieving insulin independence. Hispanicity is correlated with receiving insulin, steroids and various HLA markers: these predict less success. Processing centers related to the transplant center favor the endpoint. Daclizumab is favorable. Variables that cannot be excluded as significantly associated with this outcome are donors given steroids, HLA factors and islet beta cell counts. Again here, there is substantial imbalance between most immunosuppressants other than sirolimus and tacrolimus with most measures of procurement and processing and several recipient characteristics as well, thus preventing meaningful assessment of those immunosuppressant therapies in a multivariate model. Their univariate effects cannot be dismissed. Daclizumab is stable in this model and seems to be unfavorable for insulin independence.

Loss of insulin independence lacks sufficient events to permit multivariate modeling of factors.

The final model for complete islet failure post last infusion is:

Variable	HR	P
Recipient age (years)	0.523	<0.001
Processing/infusion center (0-Unrelated 1-Related)	0.329	0.003
Viability > 87% (0=N 1=Y)	0.317	0.012
Etanercept	0.352	0.016
Calcineurin inhibitor	0.120	<0.001

Older recipient age predicts lower risk of losing the graft. Related processing and infusion centers substantially reduce the chances of losing the last graft. Higher islet viability reduces risk of islet loss. Etanercept and calcineurin inhibitors seem favorable for persistent function.

There are significant correlations among the factors investigated for association with the primary outcomes that influence how the multivariate models operate.

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, 41% of the recipients were on at least one anti-hypertensive medication and 32% were on a lipid lowering medication. By Year 1 post last infusion, these rates increased to 52% 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 (pre-subsequent infusion, 6 months, 1 year, 2 years and 3 years post infusion) were minimal for ALT (5%), AST (4%), alkaline phosphatase (10%) and for total bilirubin (1%). There were no reports at this level for total cholesterol and 10 reports (4%) for triglycerides. There were 46 reports (16%), of a participant with an increase in their serum creatinine of greater than 0.5 mg/dL above their baseline level. Actual incidence of elevated labs might be higher if CITR reported time points were more frequent.

Adverse Events. Sixty-four percent of the islet alone recipients experienced at least one adverse event in Year 1 post first infusion, while 46% experienced one or more serious adverse events in this same period. Of the 509 adverse events reported in Year 1 post first infusion for islet alone recipients, 35% were related to the immunosuppression therapy and 33% were related to the infusion procedure. Of the 252 serious adverse events reported in Year 1 post first infusion for islet alone recipients, 28% were related to the immunosuppression therapy and 41% were related to the islet infusion procedure. Overall, a total of 440 serious adverse events were reported to the Registry as of datafile closure, with 37% of them classified as life threatening and 51% requiring an inpatient hospitalization. Sixty-five percent (286 of 440) of serious adverse events occurred in the first year following the participants' first infusion procedure. Over 27% of the serious adverse events were classified by the reporting CITR investigator as related to the islet infusion procedure and 26% related to the immunosuppression therapy. Adverse event relationships to the infusion procedure and immunosuppression regimen are determined by the local CITR Investigator. Approximately 87% of the serious adverse events resolved with no residual effects. Most of the reported serious adverse events were categorized as investigations (18%), gastrointestinal disorders (18%) and blood and lymphatic system disorders (14%) as classified by the MedDRA classifications system.

The most common serious adverse events within the first year following an islet allograft infusion are: elevated liver function tests (9% of all allograft recipients) and neutropenia (9%), followed by procedural hemorrhage (6%), abdominal pain (4%), and pneumonia (3%). Anemia, diarrhea, hypoglycemia, portal vein thrombosis, vomiting, cholecystitis, and lymphopenia occur less frequently (2% each).

Neoplasms have been diagnosed in 14 allograft recipients over the reported period of follow-up (1999-2007). None of the neoplasms were reported by the investigator as related to the islet infusion procedure. Four were reported to be related to the immune suppression medication (basal cell carcinoma, squamous cell carcinoma, ovarian cysts and papillary thyroid cancer). The most frequent type of neoplasm was squamous cell

carcinoma (N=6). Ten recipients continued their islet transplant immunosuppression regimen, two withdrew voluntarily, and two have missing follow-up.

Reported Deaths. There have been seven reports of death to the Registry for islet allograft recipients: a viral meningitis attributed death possibly related to the immunosuppressant therapy 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, another stroke more than three years post the person's only infusion, and three deaths due to unknown causes.

CONCLUSIONS

The number of centers performing clinical islet cell allograft transplants and the total number of islet cell transplants have steadily declined since 2005. However, with the anticipated start of the new Clinical Islet Transplantation (CIT) Consortium protocols in 2008, the number of new islet cell recipients is expected to rise. Islet transplantation continues to show short-term benefits of insulin independence, normal or near normal HbA_{1c} levels, sustained marked decrease in severe hypoglycemic episodes and a return of hypoglycemia awareness. Long-term primary efficacy and safety of immunosuppression as well as effects on secondary complications are less well understood and are the focus of ongoing research. The accumulated experience in islet transplantation indicates that the best candidates for islet transplantation are older recipients in better glycemic control; more IEQ's infused and larger islet size yield higher levels of good outcomes; the effects of most of the immunosuppression regimens cannot be definitively assessed in this uncontrolled setting; and the role of specialized, remote processing islet centers requires better understanding.

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.

