



2009 Scientific Summary of the Collaborative Islet Transplant Registry (CITR)

BACKGROUND AND PURPOSE

Islets of Langerhans are located in the pancreas and contain insulin producing cells (beta cells). In patients with Type 1 diabetes mellitus (T1DM), beta cells 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) is approximately 1.5 million people (National Institute of Diabetes and Digestive and Kidney Diseases. National Diabetes Statistics, 2007 fact sheet). 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 islets extracted from a deceased donor pancreas.

The National Institute of Diabetes & Digestive & Kidney Diseases funded the Collaborative Islet Transplant Registry (CITR) for data collection from North American programs to accumulate and compile the data from all completed and ongoing studies between 1999 and the present. The Juvenile Diabetes Research Foundation (JDRF) has granted additional funding to include the participation of selected European and Australian centers. CITR Annual Reports are public and can be downloaded or requested in hard copy at www.citregistry.org.

In the United States, islet transplantation is an experimental procedure that is regulated by the Food and Drug Administration (FDA). 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 glycemic control can be achieved and to assess the risks of the infusion procedure and associated immunosuppressive medication. 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. In addition, CITR developed a map of North American clinical trials that can be accessed at www.citregistry.org.

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.

Detailed follow-up data are abstracted pre-infusion and at Month 6, Month 12, and annually post infusion. At each new infusion, a new follow-up schedule is established. 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. 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. Data are also obtained through data sharing agreements with the United Network for Organ Sharing (UNOS), the Administrative and Bioinformatics Coordinating Center (ABCC) of the Islet Cell Resource Centers (ICR), and the Data Coordinating Center (DCC) of the Clinical Islet Transplant Consortium (CIT).

The Registry data exists because of the voluntary participation of the transplanting centers, with written informed consent for participation in the Registry by the islet recipients. While the Registry 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 database was closed for analysis on April 1, 2009 for data on recipients that were registered in CTR as of December 31, 2008.

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. 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.

RESULTS

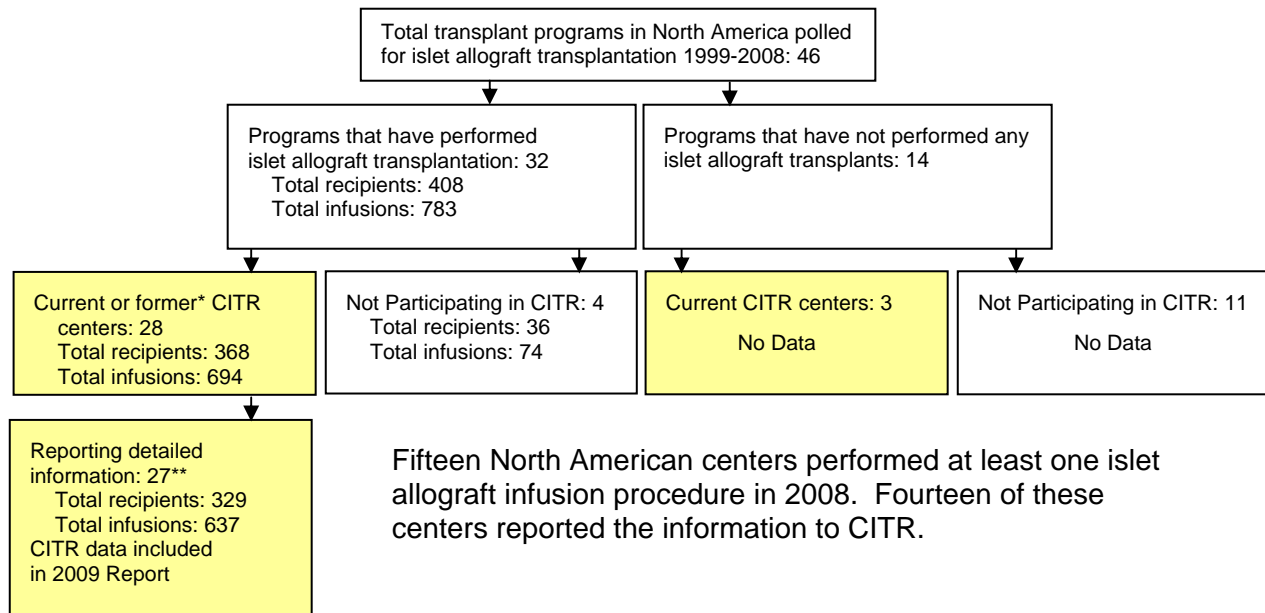
Islet Allograft Transplantation Activity 1999-2008. Forty-six North American medical institutions with an identified islet transplant program or interest in starting an islet program between 1999 and 2008 responded to a general questionnaire. Thirty-two of the 46 reported performing at least one islet allograft transplant. Exhibit A displays the activity of North American islet transplant centers for 1999-2008, including the total number of recipients and infusions, and according to the centers' participation in CTR. To the knowledge of the Registry, this table is inclusive of all human-to-human islet transplant programs in North America.

Exhibits B-1 and B-2 display the data collected from the 32 active islet transplant programs in North America and the JDRF-funded European and Australian sites from 1999 through 2008.

Three European and two Australian JDRF-funded centers joined the Registry in 2006-2008 and contributed data for this report. Pooling the reported data from the North American and JDRF centers, the Registry comprises 412 allograft recipients with detailed data reported as of the data cut-off, and 828 infusion procedures derived from a total of 905 donors. One hundred seven of the recipients (26%) received a single islet infusion, 202 (49%) received two, 95 (23%) received three, and eight (2%) received a total of four islet infusions. On average, recipients received a total of 842×10^3 (SD 376×10^3) total islet equivalents (IEQs), or 13×10^3 (SD 6.0×10^3) IEQs/kilogram body weight.

Of the total 412 recipients included in this report, 347 (84%) were recipients without a previous kidney transplant who received one or more islet-alone infusions (IA), while 65 recipients (16%) had previously received a kidney transplant (IAK).

Exhibit A
North American Islet Allograft Transplant Centers, Recipients and Infusions
Total Performed and Total Reported to CITR 1999-2008



Fifteen North American centers performed at least one islet allograft infusion procedure in 2008. Fourteen of these centers reported the information to CITR.

* Former CITR centers (N=3) are those that reported data to CITR then subsequently stopped performing islet cell transplants and discontinued CITR participation.

** One center with three allograft participants who did not provide CITR consent.

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 1999-2008

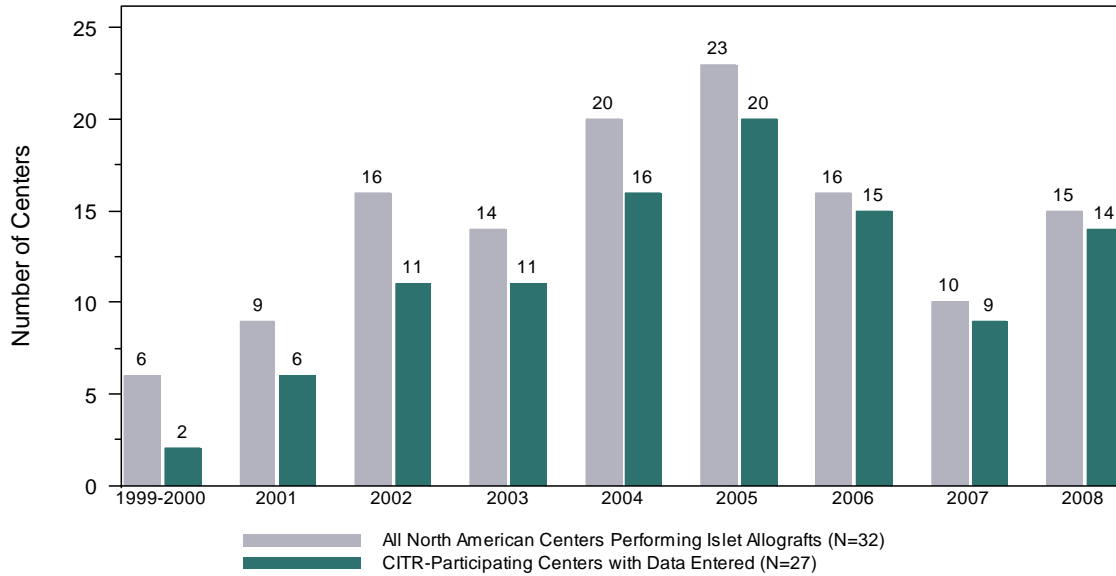
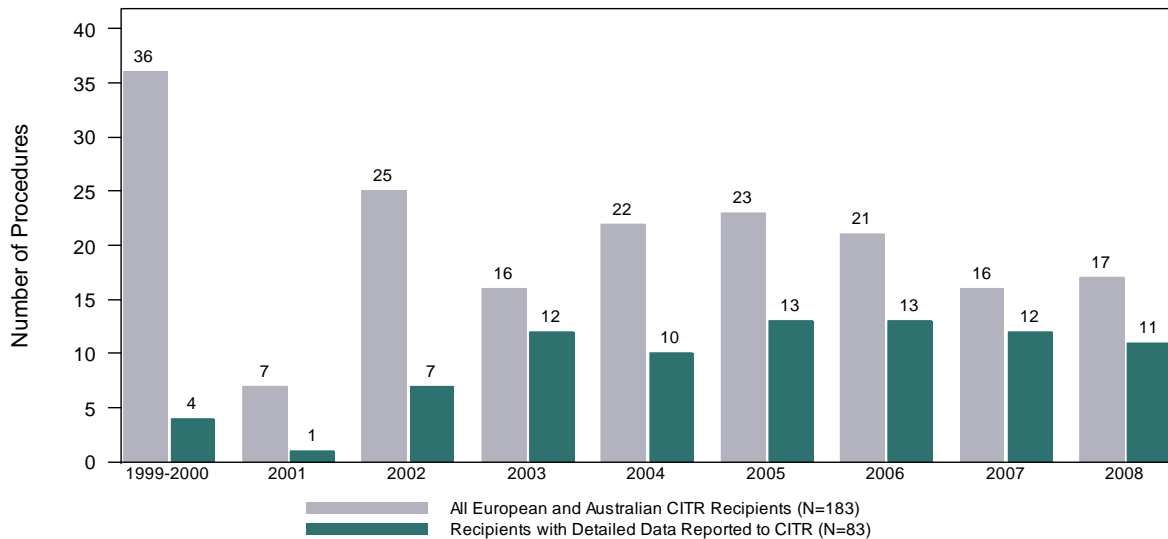


Exhibit B – 2
Total Number of Islet Allograft Recipients and Recipients with Detailed Data
Reported to CITR by Year of First Islet Allograft Infusion CITR
Participating European and Australian JDRF Centers 1999-2008



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 28 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 24 kg/m² (range 16 to 32). About 63% of the recipients are female. There is limited racial and ethnic diversity among the participants with this data reported.

Approximately 35% of the 412 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 85% had an 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 19 years (SD 13.5). The mean fasting blood glucose for all participants was 173 mg/dL (SD 88), mean HbA_{1C} was 7.7% (SD 1.3), and the mean basal C-peptide was 0.1 ng/mL (SD 0.26).

Thirty three percent of islet recipients do not have reported data on autoantibody (GAD-65, IA-2, and Insulin) levels. Of known data, 73% have at least one positive autoantibody measurement. Measurement of autoantibody levels is strongly encouraged for all potential islet transplant recipients.

Donor Information. There were no living donors. The mean age of donors was 44 years (range 1 to 75) and the mean body mass index was 29 kg/m² (SD 6.5). Approximately 59% of the donors were male, 10% were Hispanic and 90% were white. Fifty-six 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 19% had a history of alcohol dependency.

Thirty-two percent of the donors received a transfusion during hospitalization, while only 6% received a transfusion intraoperatively. Fifty nine percent of the donors received steroids, 40% of the donors received insulin and 95% received at least one vasopressor during the donor's terminal hospitalization. There was a report of one donor testing positive for anti-HBC, and one testing positive for RPR-VDRL. The mean serum creatinine of the donors was 1.1 mg/dL.

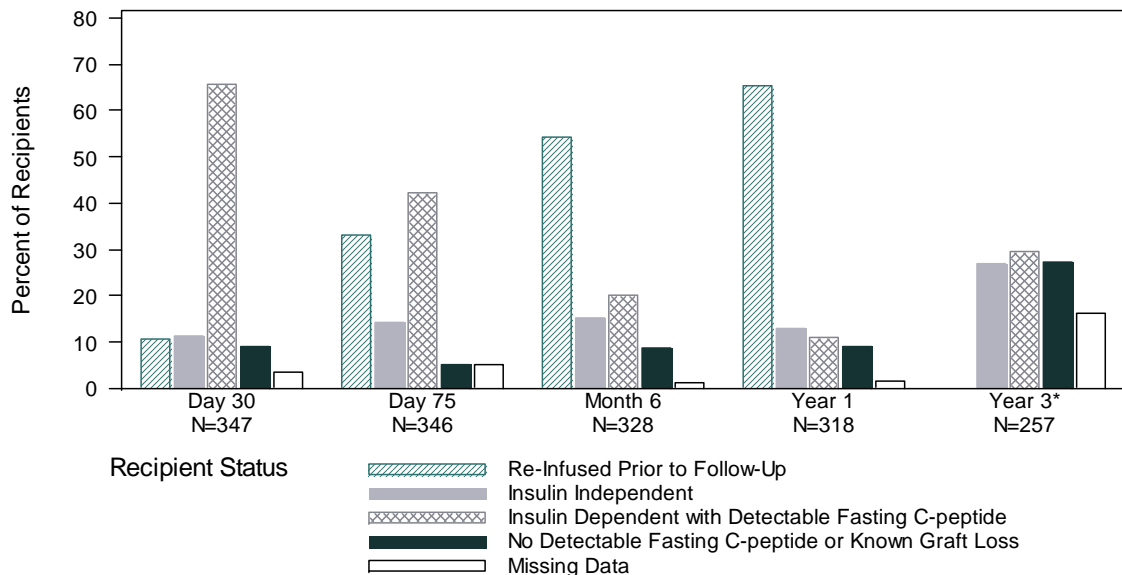
Pancreas Procurement. In 63% of the 905 pancreas procurement procedures, the pancreas procurement team was not related/affiliated with the processing/transplant team, while 91% of the processing procedures took place at the same institution as the islet transplant center. The mean time from cross clamp to pancreas recovery was 44 minutes (SD 22) while the mean cold ischemia time was 7.3 hours (range 1 to 27). UW and Two Layer were the most common (85%) methods used for pancreas preservation.

Liberase HI was the collagenase type used during most islet processing (77%) followed by NB1 (18%). All of the pancreata processed used a density gradient for islet purification. Fifty four percent of islets were placed in culture, defined as six or more hours in a specially prepared nutrient medium. When cultured, the median culture time was 27 hours (range 6 to 96). Of the 905 islet preparations reported to CITR, thirteen final preparations showed a positive aerobic culture (1.7%), five showed a positive anaerobic culture (0.8%), four showed a positive fungal culture (0.5%), and one tested positive for mycoplasma (0.2%).

Immunosuppression Therapy. The majority (52%) of the islet transplant alone recipients at the time of first infusion were on a Daclizumab, Sirolimus, and Tacrolimus only immunosuppression regimen. Daclizumab was the sole antibody used in 59% of first infusions. Anti-thymocyte globulin was given alone or in combination in 14% of first infusions. Substantial shifts away from anti-IL2 induction and away from Sirolimus / Tacrolimus maintenance have occurred over the last five years.

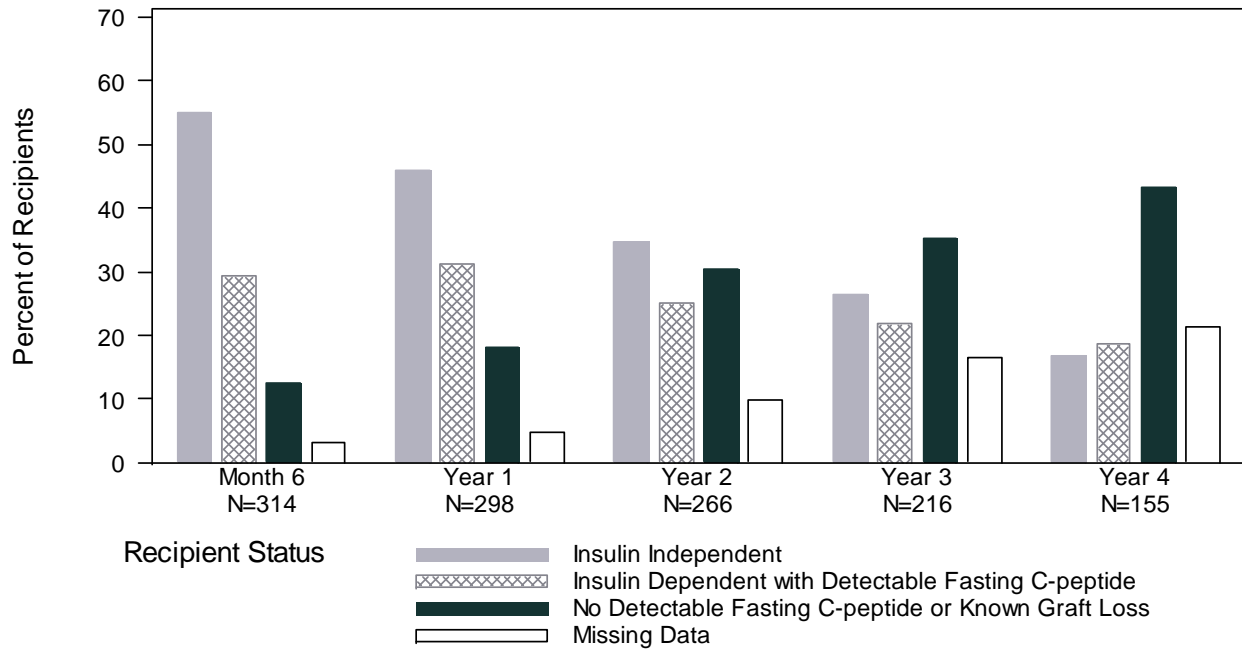
Graft Function. After the first infusion, increasing proportions of islet-alone recipients are re-infused: 11% by Day 30, 33% by Day 75, 54% by Month 6, and 65% by Year 1 (Exhibit C-1). The proportion that is insulin independent without re-infusion remains fairly constant at 11-15% throughout the first 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 347 IA recipients, 74% have at least three years follow up post first infusion, at which time, regardless of the total number of infusions received, about 27% are insulin independent, 30% are insulin dependent with detectable C-peptide, 27% have no detectable C-peptide, and 16% have missing data (required but not yet reported).

**Exhibit C – 1
Insulin Independence, Insulin Dependence,
Absence of Fasting C-peptide, or Re-Infusion
Post First Infusion
Islet Alone Recipients**



*Year 3 status regardless of re-infusion

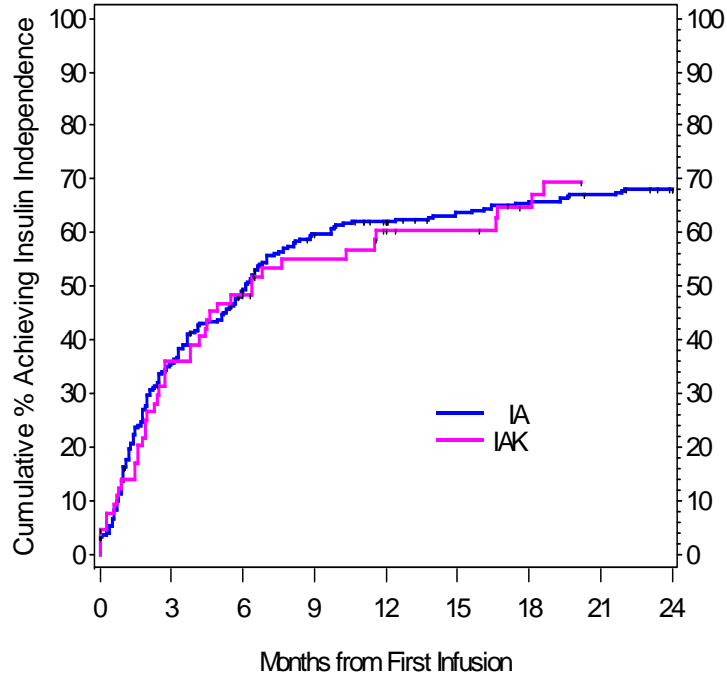
Exhibit C – 2
Insulin Independence, Insulin Dependence
or Absence of Fasting C-peptide
Post Last Infusion
Islet Alone Recipients



Analyzed from last infusion (Exhibit C-2), the percentage of all IA recipients that are insulin independent declines steadily from 55% at Month 6 to 16% at Year 4. The proportion with loss of islet function (reported graft failure or no detectable C-peptide) increases steadily from 12% at Month 6 to 42% at Year 4. A stable 19-31% retains graft function with exogenous insulin over the four years; the percentage of missing data increases over time.

Cumulative event rates of achieving insulin independence after first infusion regardless of the number of infusions given is an indicator of the rate of engraftment under the real-time conditions of competing events including graft loss, islet resource availability, and myriad biologic factors, some of which are characterized in the CITR data and some are not. It is notable that the cumulative rate of achievement of insulin independence follows the general shape of engraftment curves for solid organs, but with a slower initial slope, indicative of multiple infusions. Achievement of insulin independence is indistinguishable between islet alone and islet after kidney patients. As incidence or cumulative rates of ever achieving insulin independence after islet transplantation, 62% 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 68% (Exhibit D).

Exhibit D
Achievement of Insulin Independence After Islet Transplantation
Not Censored at Re-Infusion or Graft Loss
Post First Infusion
Islet Alone vs. Islet After Kidney



Over time there is a decrease in the sustainability of insulin independence (Exhibit E-1). For islet alone participants who ever achieved insulin independence, 70% have retained this status one year after achieving it and this decreases to 45% at three years. Recipients transplanted since 2005 retained insulin independence significantly longer than those transplanted in 1999-2004 (Exhibit E-2).

Exhibit E – 1
Persistence of Insulin Independence
Allograft Recipients Achieving Insulin Independence
Post Last Infusion
Islet Alone vs. Islet After Kidney

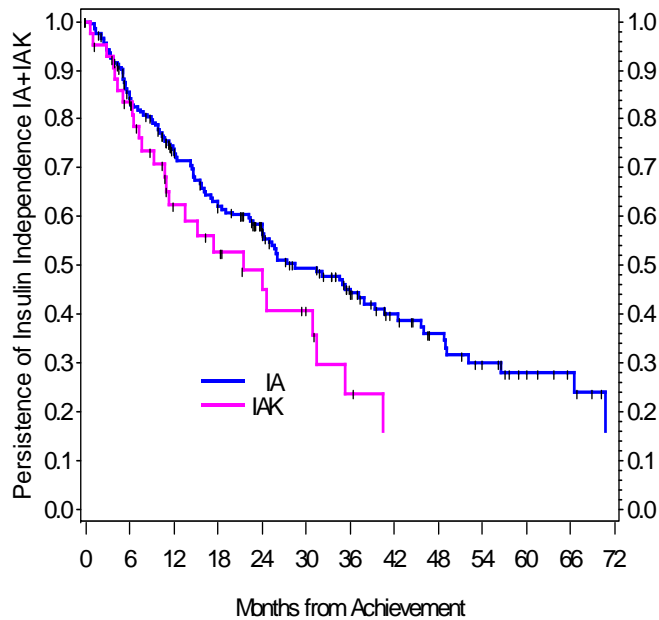


Exhibit E – 2
Persistence of Insulin Independence
Allograft Recipients Achieving Insulin Independence
Post Last Infusion
by Era of First Infusion

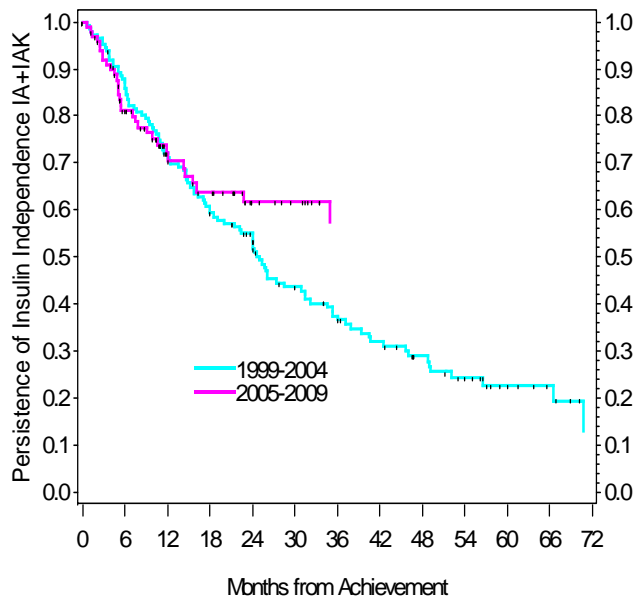
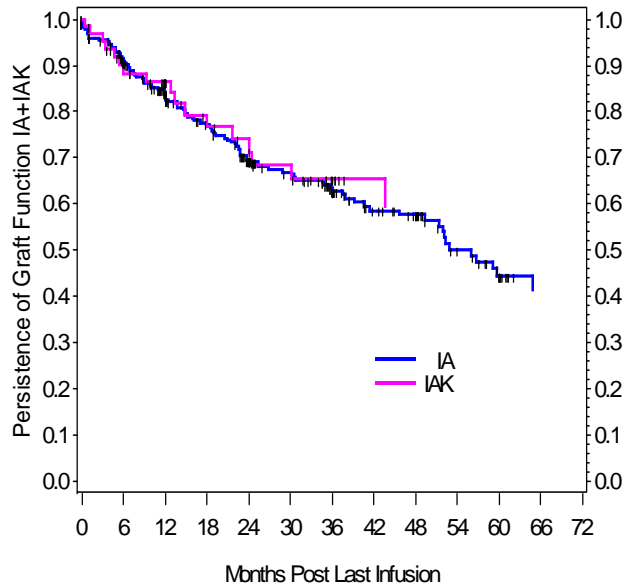


Exhibit F
Persistence of Islet Graft Function
All Allograft Recipients
Post Last Infusion
Islet Alone vs. Islet After Kidney



Similarly, graft function is lost over time. Viewed as Kaplan-Meier survival estimates (Exhibit F) 65% of IA recipients retain function by Year 3 post last infusion.

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 C-peptide values substantially increase. The percent of IA recipients with C-peptide >0.5 ng/mL increases from 7% pre-infusion to 77% at Month 6 post last infusion with 45% retaining this level of function at Year 3 post last infusion. These trends are seen both overall and by total number of infusions. Results are affected by the recipients' transient insulin status and whether or not they ever achieved insulin independence.

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, the percent of IA recipients with HbA_{1c} <6.5% and absence of severe hypoglycemic episodes increases from 2% pre-infusion to 51-60% at Year 1 post last infusion with a subsequent decline to 20-45% by Year 4 post last infusion (Exhibit G-1). In these ranges, 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. Hypoglycemia awareness is also markedly improved and is eroded only by loss of graft function or loss to follow-up (Exhibit G-2).

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

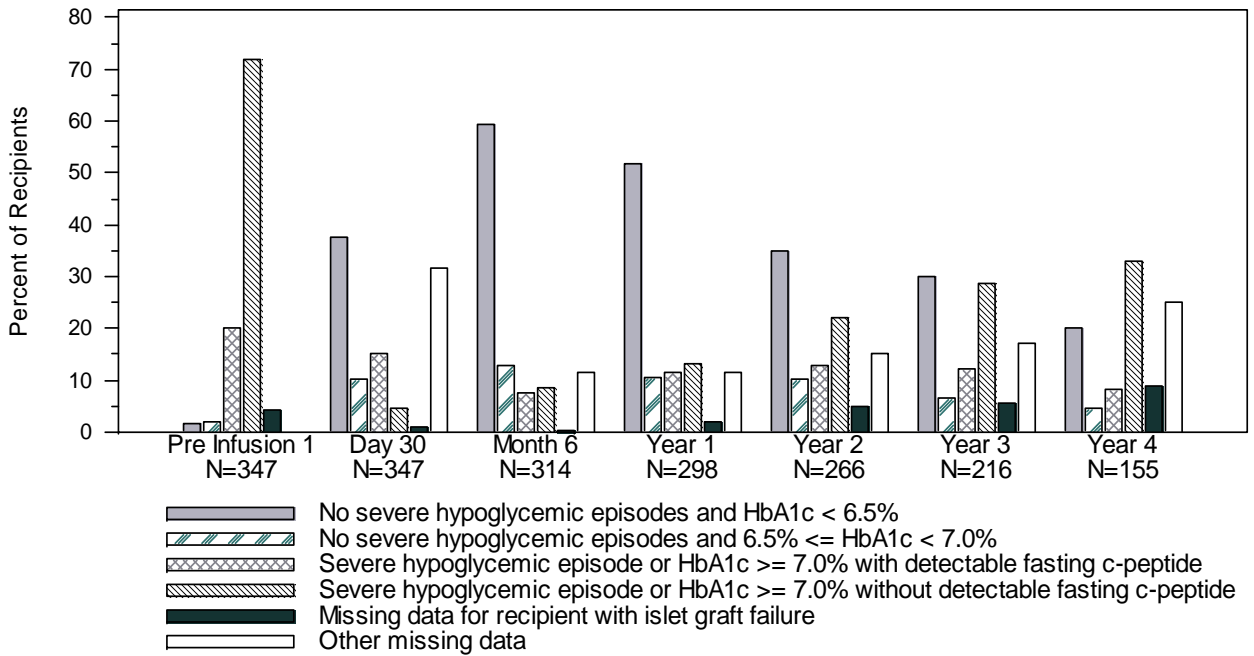
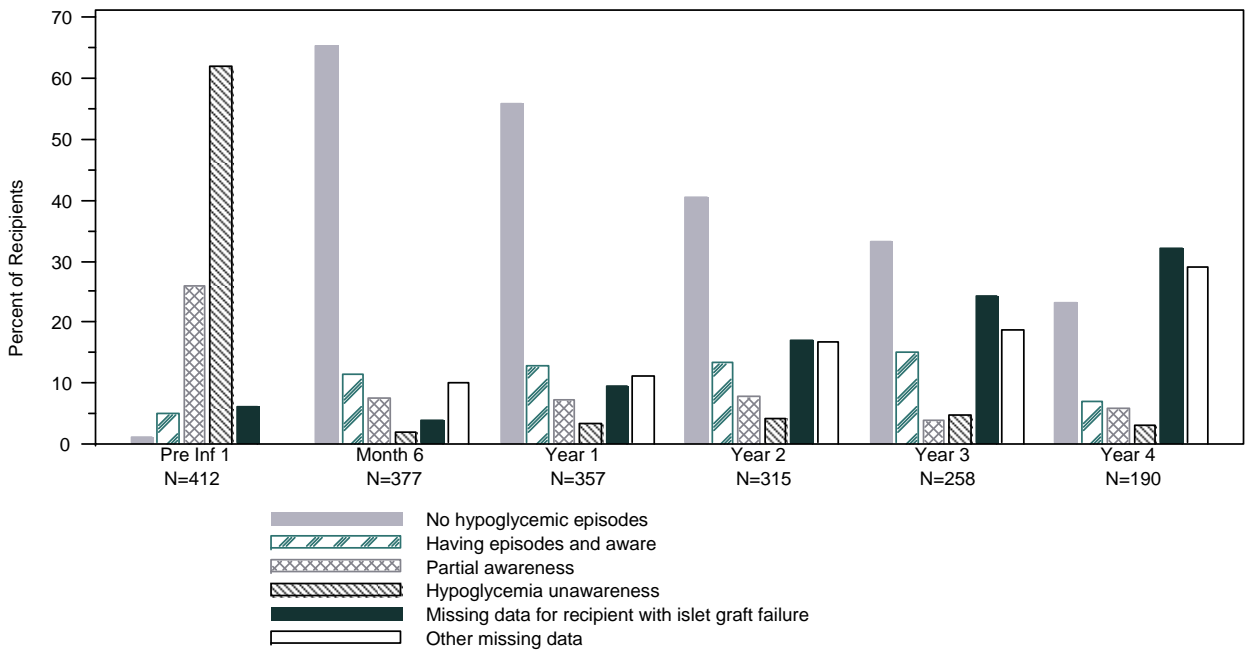


Exhibit G – 2
Hypoglycemia Status Pre First Infusion and Post Last Infusion
All Allograft Recipients



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 achieving insulin independence post last infusion (209 events / 341 recipients) is:

Variable	HR	p
Baseline HbA _{1c}	0.89 Lower HbA1c favorable	0.03
Procurement/infusion center (0=unrelated 1=related)	1.32 Related is favorable	0.08
Processing/infusion center (0=unrelated 1=related)	2.88 Related is favorable	0.002
Daclizumab (0=N 1=Y)	1.79 Daclizumab is favorable	0.005

Baseline HbA_{1c}, baseline weight, baseline BMI, baseline daily insulin, fasting glucose, and number of daily injections are substantially mutually correlated: 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. The processing center being related to the transplant center is favorable. Daclizumab is favorable. Variables that cannot be excluded as significantly associated with this outcome are donor's given steroids, HLA factors and islet beta cell counts. 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 favorable for insulin independence.

The final model for complete islet failure post last infusion (111 events / 341 recipients) is:

Variable	HR	p
Age	0.68 Higher age is favorable	<0.001
Processing/infusion center (0=unrelated 1=related)	0.42 Related is favorable	0.003
Etanercept (0=N 1=Y)	0.47 Etanercept is favorable	0.02
Calcineurin Inhibitor (0=N 1=Y)	0.26 Calcineurin inhibitor is favorable	0.003

Older recipient age predicts lower risk of losing the graft. Related processing and infusion centers substantially reduce the chances of losing the last graft. Etanercept and calcineurin inhibitors are confirmed as 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.

Concomitant Medications. Prior to the first infusion, 43% of the recipients were on at least one anti-hypertensive medication and 34% were on a lipid lowering medication. By Year 1 post last infusion, these rates increased to 53% and 61%, respectively.

Adverse Events. CTR is the leading resource for adverse event information in islet transplant recipients. Sixty-two percent of the islet alone recipients experienced at least one adverse event in Year 1, while 44% experienced one or more serious adverse events in this same period. Of the 594 adverse events reported in Year 1 post first infusion for islet alone recipients, 32% were related to the immunosuppression therapy and 27% were related to the infusion procedure. Of the 312 serious adverse events reported in Year 1 post first infusion for islet alone recipients, 29% were related to the immunosuppression therapy and 33% were related to the islet infusion procedure.

Overall, a total of 592 serious adverse events were reported to the Registry as of datafile closure, with 29% of them classified as life threatening and 52% requiring an inpatient hospitalization. Sixty-two percent (365 of 592) of serious adverse events occurred in the first year following the participants' first infusion procedure. Twenty-five percent of the serious adverse events were classified by the reporting CTR investigator as related to the islet infusion procedure and 29% related to the immunosuppression therapy. Approximately 82% of the serious adverse events resolved with no residual effects. Most of the reported serious adverse events were categorized as gastrointestinal disorders (17%), investigations (14%) and blood and lymphatic system disorders (13%) as classified by the MedDRA classifications system.

Neoplasms have been diagnosed in 21 of the 412 islet recipients. None were related to the islet infusion procedure while nine may have been related to the immunosuppression therapy (basal cell carcinoma (x2), squamous cell carcinoma (x3), breast cancer, ovarian cysts, and papillary thyroid cancer (x2)). The most frequent type of neoplasm was squamous cell carcinoma (nine recipients). Seventeen recipients continued their islet transplant immunosuppression regimen; two withdrew voluntarily; and two have missing follow-up.

Reported Deaths. There have been nine reports of death to the Registry for islet allograft recipients; a viral meningitis attributed death possibly related to the immunosuppressant therapy occurring three years following the person's last islet infusion, a drug toxicity (acute methadone and diphenhydramine) 70 days post the person's last infusion, a stroke two years post the person's last infusion, another stroke three years post the person's last infusion, a death due to acute respiratory distress syndrome five years post last islet infusion, pneumonia eight years after the person's last infusion, diabetic ketoacidosis six years after the person's last infusion, atherosclerotic coronary artery disease 16 months after the person's last infusion and one death due to unknown causes.

CONCLUSIONS

In the years since 2005, fewer North American centers performed an islet transplant and there were half as many islet transplant recipients in 2008. However, more centers transplanted and more people received an islet transplant in 2008 compared to 2007. With the continuation of Clinical Islet Transplantation (CIT) Consortium protocols that began 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. The accumulated experience in islet transplantation indicates that the best candidates for islet transplantation are older recipients in better glycemic control; close relationships between procurement, processing, and transplant teams as well as use of Daclizumab, Etanercept, and Calcineurin inhibitors are associated with favorable outcomes. Not all other factors can be discounted as favorable.

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November 2009

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.

