

2006 Scientific Summary of the Collaborative Islet Transplant Registry (CITR)

Background. 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 T1DM in the United States (US) (all ages, 2004) is approximately 650,000-1,300,000 people. Exogenous insulin replacement therapy has been the only method of treatment for this disease. For patients with T1DM and poor kidney function, a whole pancreas transplant is sometimes performed. An alternative procedure uses insulin-producing cells (islets) extracted from a donor pancreas. These are implanted typically via the portal vein in the liver, so that the islets produce insulin as needed by the recipient.

Islet transplantation is an experimental procedure in the US that is regulated by the Food and Drug Administration (FDA). Approximately, 40 transplant programs in the US are conducting this procedure, or are in the process of starting a program. Typical patients eligible for this procedure include those who have T1DM for more than five years, are between 18 and 65 years of age, and have poor diabetes control despite intensive efforts being made in close collaboration with a qualified diabetes care team. 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%).

Most ongoing studies differ minimally in the entry criteria for patients and in the types of immunosuppression therapy used to prevent rejection of the islet cells in the body. 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 public website and through the National Library of Medicine's developed website www.clinicaltrials.gov.

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). 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 performed in North America. Each year the Registry provides a complete analysis of the cumulative data to date since 1999. The third report, published in 2006, summarizes information on patients who received one or more islet cell transplants between 1999 and 2005. All CITR reports are public and can be downloaded or requested in hard copy at www.citregistry.org.

Data contained in this summary must be interpreted cautiously. Even with the efforts of the 23 participating centers, the total number of reports is still small. As with any registry, a number of potential biases may exist, including selective reporting and differences in clinical care and decision-making. Islet transplant recipient data for this summary reflect cumulative data entered by the islet transplant centers on participants from January 1, 1999 through December

31, 2005. These data were reviewed by the CITR Coordinating Center for quality assurance, errors and data outliers. Data queries were identified and the database was updated by the islet transplant centers and closed for analysis on April 3, 2006 for the recipients that had been registered for CITR as the December 31, 2005 participant registration closure date.

Status of Islet Allograft Transplantation in North America. CITR collects basic information from all islet transplant centers in North America. Forty-two islet transplant programs were sent a questionnaire asking for information. All 42 programs responded and 31 of the 42 programs had been active during 1999-2005, performing at least one islet allograft transplant. The remaining programs (N=11) had not transplanted yet, or were in the process of starting their islet allograft transplant program. The table below displays the data collected from the 31 active islet transplant programs in North America for 1999-2005. To the knowledge of the Registry, this table is inclusive of all islet transplant programs in North America.

Exhibit A
Summary of North American Islet Allograft Transplantation Activity

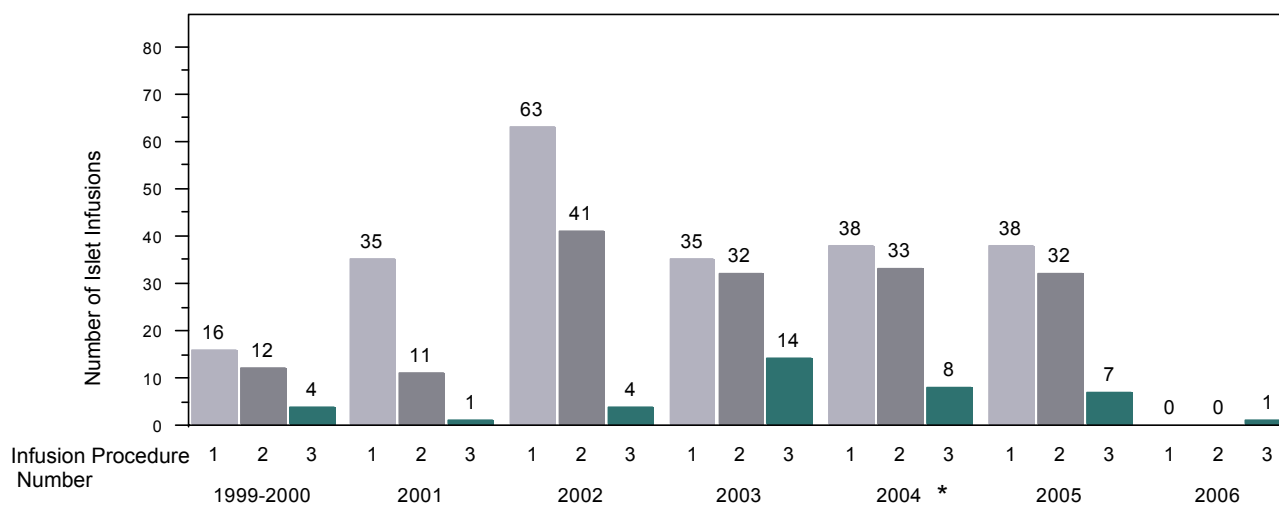
All Islet Transplant Programs in North America	Number of Human Islet Infusion Procedures Conducted	Number of Patients Receiving Their First Infusion
Total	593	319
1999	18	10
2000	32	21
2001	65	45
2002	142	82
2003	106	45
2004	110	53
2005	120	63

Registry Data Collection. The focus of the Registry is the collection and analysis of islet allograft transplants. From 1999-2005, 31 islet transplant programs have conducted 593 islet infusion procedures in 319 recipients (Exhibit A). CITR has information from 23 islet transplant programs on 225 of the 319 allograft recipients (71%) and 425 of the 593 infusion procedures (72%). Sixty-four of the recipients (28.4%) received just one islet infusion, 122 (54.2%) received two, 38 (16.9%) received three, and one (0.4%), received a total of four islet infusions. On average, recipients received a total of 814,378 (SD 368,620) total islet equivalents (IEQs), or 12,486 IEQs/kilogram body weight (SD 5,731).

Of the 225 recipients, 203 (89%) were recipients without a previous kidney transplant who received an islet infusion(s) (islet alone recipients), while 22 recipients (10%) had previously received a kidney transplant and received an islet infusion(s) after a kidney transplant. There were two recipients (1%) of an islet autograft for pancreatitis voluntarily reported to the Registry, even though the number of autografts performed in the US is much higher (>300 recipients ever receiving an islet autograft transplant).

Exhibit B summarizes the total number of islet allograft infusion procedures conducted and entered in the CITR database by year and by infusion procedure number. For example, in 2001, 35 participants received their first islet infusion, 11 received their second islet infusion, and one person received their third islet infusion.

Exhibit B
Total Number of Islet Allograft Infusion Procedures Conducted and Entered in the CITR Database by Year and by Infusion Procedure Number



*One person received a fourth infusion in 2004.

Participant Characteristics. The median age of the islet transplant participant is 42.3 years (range 23.0 to 65.1) and the median duration of diabetes is 29 years (range 4 to 51). The median weight of the participant is 65 kg (range 35.0 to 98.1) and the median body mass index (BMI) is 23.3 kg/m² (range 15.5 to 31.6). Over 68% of the participants are female and the participants have limited racial and ethnic diversity.

Approximately, 38% of the islet transplant participants were on an insulin pump prior to their first infusion and 92.6% of the participants were on the pump or were taking three or more insulin injections per day. At baseline, over 89% of the participants have a basal C-peptide < 0.5 ng/mL (C-peptide results at the time closest to transplant were used for this analysis and do not necessarily represent the typical value for the participant) and over 78% have an HbA_{1c} > 6.5%. The mean daily insulin requirement of participants prior to their first infusion procedure was 37.7 units (SD 14.0) and the subset on intensive insulin therapy had received intensive therapy for a mean of 18.3 years (SD 12.6). The mean fasting blood glucose for all participants was 169.7 mg/dL (SD 88.0), mean HbA_{1c} was 7.7% (SD 1.3), and their mean basal C-peptide was 0.1 ng/mL (SD 0.3).

Participant baseline characteristics prior to first infusion by the total number of infusions received were evaluated. On comparison, participants who had received a total of three infusions were younger, their duration of diabetes was shorter, they had a higher BMI, required a higher baseline daily insulin requirement, had a much higher fasting blood glucose and HbA_{1c} and had a lower PRA percentage than those participants who had one or two infusion procedures.

Donor Information. The median age of the deceased donor was 44 years (range 8 to 74) and the median body mass index was 28.2 kg/m² (range 13.3 to 59.8). The median time from cross clamp to pancreas recovery was 33 minutes (range 0 to 127) while the median cold ischemia time was 7.0 hours (range 1.1 to 27.0). Approximately 58% of the donors were male, 9% were Hispanic and 90% were white. Fifty-four percent of the donors had a cerebrovascular/stroke as cause of death while 31% experienced a head trauma. Approximately 31% of the donors had a history of hypertension and 17% had a history of alcohol dependency.

Thirty-six percent of the donors received a transfusion prior to organ procurement, while only 6% received a transfusion during the organ procurement surgery. Sixty-six percent of the donors received steroids and 39% of the donors had received insulin. Over 96% of the donors 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 median serum creatinine of the donors is 1.0 mg/dL, total bilirubin 0.7 mg/dL, AST 37.0 IU/L, ALT 30.0 IU/L, serum lipase 27.5 IU/L and serum amylase 72.0 IU/L.

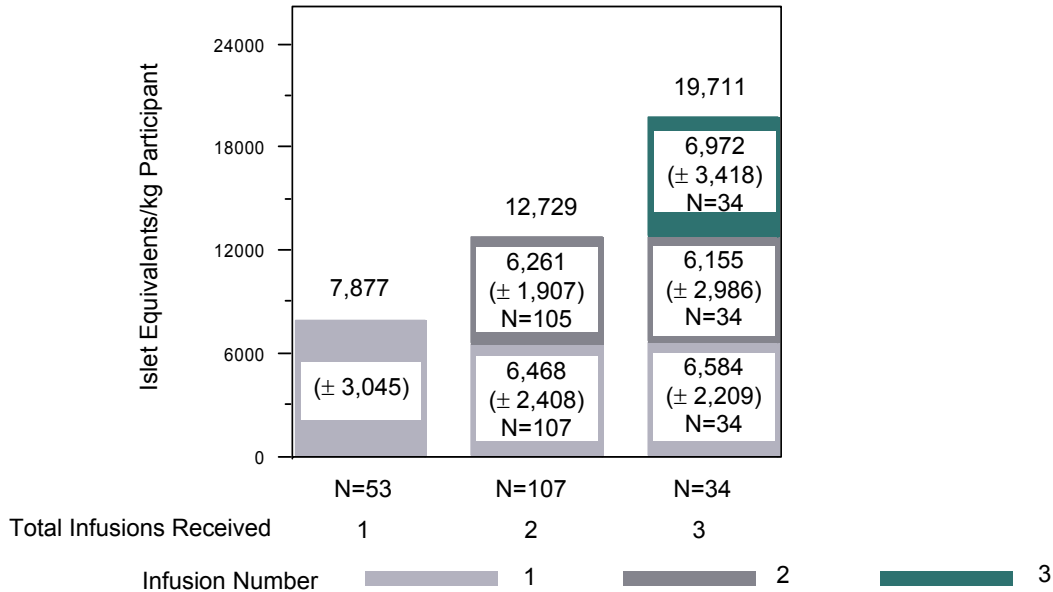
Pancreas Procurement. In over 62% of the pancreas procurement procedures, the pancreas procurement team was not related/affiliated with the processing/transplant team, while 88.5% of the processing procedures took place at the same institution as the islet transplant center. The median duration of cold ischemia was 7 hours (range 1.1 to 27.0). UW, Two Layer (UW and PFC, N=164; HTK and PFC, N=3), and UW followed by Two Layer were the most common methods used for pancreas preservation. Other preservation solutions used in conjunction or in absence of UW and/or PFC included HTK, Eurocollins, P Phase 2, and Lactated Ringer's solutions.

Liberase HI was the collagenase type used during most islet processing (95%) followed by Thermolysin plus Collagenase P (2%), and custom Liberase Blend (1%). All of the pancreata processed used a density gradient for islet purification. Almost 60% of the islet preparations were placed in culture for some period of time. The Registry defines "culture" as any specially prepared nutrient medium. The median culture time was 28 hours (range 1.5 to 84.0). Of the 418 preparations reported to CITR, six final preparations showed a positive aerobic culture (1.5%), four showed a positive anaerobic culture (1.4%) and three showed a positive fungal culture (0.8%).

Total islet equivalents in the final product were plotted versus cold ischemic time, donor body mass index, and donor age. Of these correlations, there is indication that donor body mass index has a statistically significant correlation with the total number of islet equivalents in the final product (Pearson correlation coefficient: $r=0.3133$, $p<0.0001$).

Exhibit C provides a summary of the total number of islet equivalents/kg participant weight for participants who received only one infusion (N=53), for those who received a total of two infusions (N=107) and for those who received a total of three islet infusions (N=34). Nine participants were excluded from this Exhibit, as they did not have islet equivalents reported and/or were missing a reported weight.

Exhibit C
Mean Number of Islet Equivalents/kg Participant (\pm SD) by
Total Number of Infusions Received
(Participants with a Total of 1 Infusion, 2 Infusions, and 3 Infusions)



Immunosuppression Therapy. The majority of the islet transplant alone recipients at the time of first infusion were on a Daclizumab, Sirolimus, and Tacrolimus immunosuppression regimen (61.1%). However, a number of other immunosuppression regimens (N=18) have been used by the islet transplant centers and are listed in Exhibit D.

Exhibit D
Immunosuppression Regimen at Time of First Infusion

	Overall	
	N	%
Total	203	100.0
Sirolimus + Tacrolimus + Daclizumab	124	61.1
Sirolimus + Tacrolimus + Daclizumab + Infliximab	17	8.4
Sirolimus + Tacrolimus + Daclizumab + Alemtuzumab	9	4.4
Sirolimus + Tacrolimus + Basiliximab + Etanercept	9	4.4
Sirolimus + Tacrolimus + Daclizumab + 15-deoxyspergualin	5	2.5
Sirolimus + Tacrolimus + Daclizumab + MMF + Methylprednisolone + Anti-thymocyte Globulin + Etanercept	5	2.5
Neoral Cyclosporine + Methylprednisolone + Everolimus + Anti-thymocyte Globulin + Etanercept	4	2.0
Sirolimus + Tacrolimus + Daclizumab + Anti-thymocyte Globulin	3	1.5
Sirolimus + Tacrolimus + Daclizumab + MMF	3	1.5
Sirolimus + Tacrolimus + hOKT3γ-1 (Ala-Ala)	3	1.5
Sirolimus + Tacrolimus + Alemtuzumab + Etanercept	3	1.5
Other Immunosuppression Regimen Therapies	9	4.4
Missing Information on Immunosuppression	9	4.4

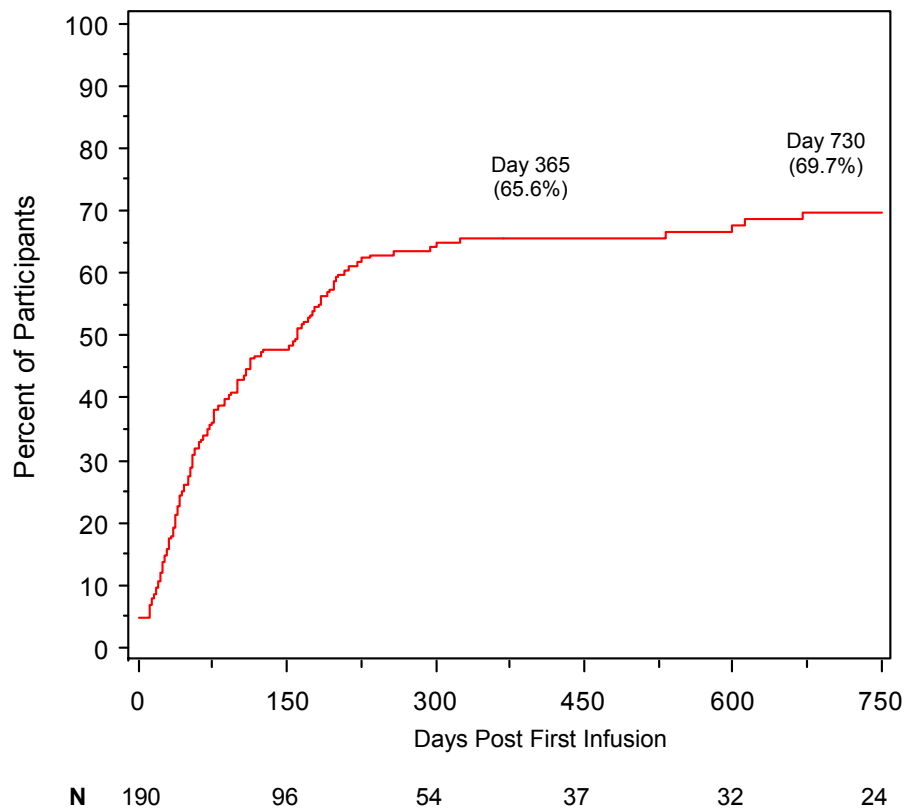
Medications and Adjunctive Therapy. Prior to the first infusion, almost 39% of the recipients were on at least one anti-hypertensive medication and over 24% were on a lipid lowering medication. By Year 1 post last infusion, these rates increased to over 48% and over 63%, respectively. Percentages are based on participants with complete medication information. For adjunctive therapies, at the time of their first infusion, over 98% of recipients used an antibiotic, 92.5% used antivirals, 88.9% used Heparin (including Heparin used during the infusion procedure), and 87.4% used vitamin supplements. The most common adjunctive therapies used during follow-up included vitamin supplements (11.9% at Month 6 and 11.0% at Year 1) and Pentoxifylline (9.3% at Month 6).

Graft Function. Following the first infusion procedure, 50.0% of participants were insulin independent six months later, with 49.4% insulin independent at one year following this first infusion. When analyzing insulin independence rates after the participant's last infusion procedure, 56.7% were insulin independent at six months, while this rate drops to 51.4% at one year. At six months and one year post the last infusion procedure, participants with a total of

two infusions have the highest insulin independence rates of 60.2% and 54.4%, respectively, compared to those with only one islet infusion (52.1% and 50.0%) and those with three islet infusions (54.5% and 46.4%).

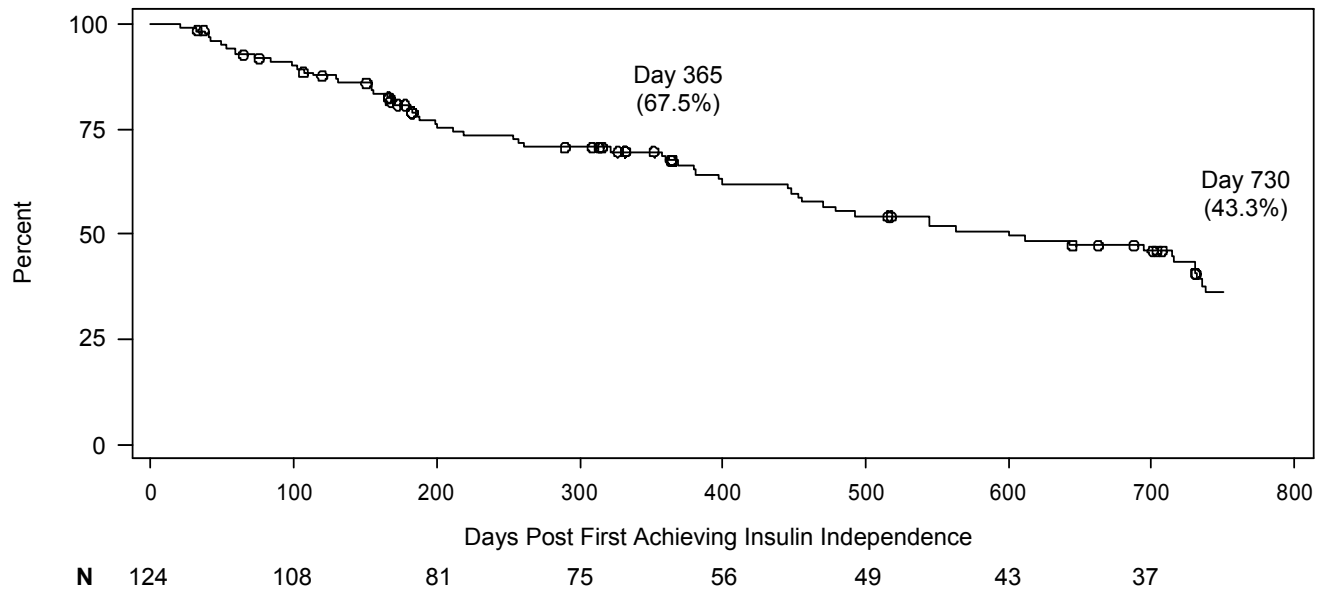
When determining if a participant ever achieves insulin independence (for 14 or more days) after receiving at least one islet infusion, at one year 65.6% of the participants have achieved insulin independence, and by year two this increases slightly to 69.7% (Exhibit E). However, no recipients have achieved insulin independence any longer than 200 days from the last infusion procedure. Stratified by the total number of infusions received when achieving insulin independence, rates at Day 75 were highest among those with two infusions (52.2%) and three infusions (46.6%). At Day 180, rates increase for all three groups to 56.1% for two infusions, 51.1% for three infusions, and 28.7% for recipients achieving insulin independence with one infusion.

Exhibit E
Percent of Participants Ever Achieving Insulin Independence



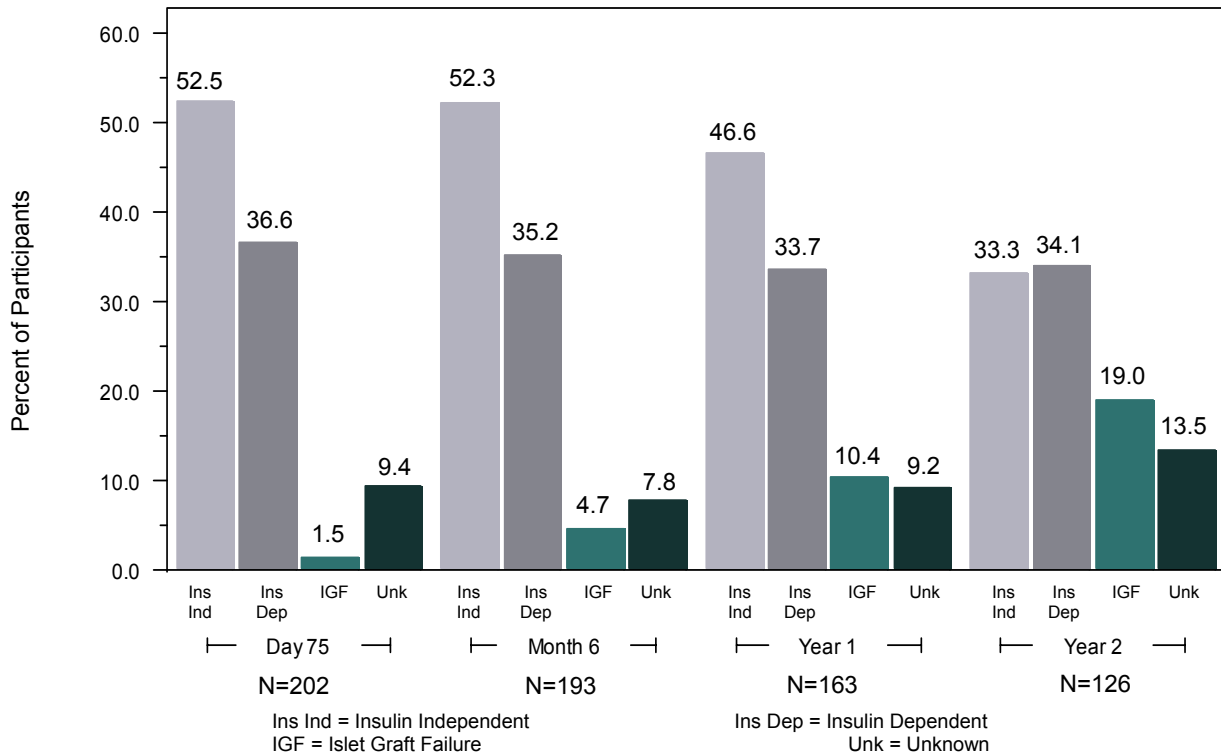
Over time there is a decrease in the sustainability of insulin independence. For all participants who have ever achieved insulin independence, only 67.5% have remained in this status one year after achieving it and this decreases to 43.3% at two years (Exhibit F). This decline is also seen by total number of infusion procedures conducted to achieve insulin independence.

Exhibit F
Time to Return to Insulin Dependence (≥ 14 Days of Insulin Use)
Among Insulin Independent Participants



A decrease in insulin independence and sustainability is also seen in Exhibit G, where at Day 75 post last infusion, rates are around 52%, then drop to 47% at one year and further drop to 33% at two years.

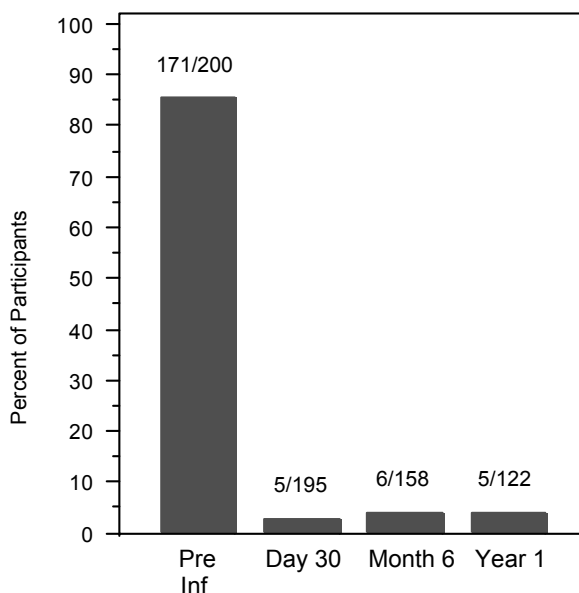
Exhibit G
Insulin Status (%) by Follow-up Visit Post Last Infusion



Changes In Islet Graft Function. For 121 participants with complete reporting of changes in islet graft function, there have been a total of 52 participants reported with one or more changes in their islet graft function (43.0%). Thirty-two participants (26.4%) have experienced islet graft failure. On average, complete loss of islet graft function occurred in these 32 participants 506 days (SD 429 days) after receiving their first islet infusion, while the median time to complete loss of islet function is 385 days.

Severe Hypoglycemic Events. As reported in last's year Annual Report, there continues to be a striking decrease in the number of severe hypoglycemic events that have occurred subsequent to the participant's first infusion procedure (Exhibit H). Over 85% of participants experienced one or more severe hypoglycemic events prior to their first infusion. This decreased to 2.6% up to 30 days post their first infusion and then to 3.8% in months 1-6 and 4.0% in months 6-12 post last infusion. All participants that experienced a severe hypoglycemic event during follow-up were on insulin at the time of the event.

Exhibit H
Percent of Participants with One or More Occurrences of Severe Hypoglycemic Episodes Pre First Infusion and Follow-Up Post First Infusion



Metabolic Measures. After the first infusion procedure, participant's fasting blood glucose values and HbA_{1C} decreased over time, while basal C-peptide values increased. This trend is seen within each of the cohort group of participants (with one, two and three infusions). At one year following the last infusion procedure, participants who ever achieved insulin independence have a mean fasting blood glucose of 111.5 mg/dL (SD 30.4), a basal C-peptide of 1.1 ng/mL (SD 0.65) and an HbA_{1C} of 6.0% (SD 0.8). Those who never achieved insulin independence have a higher fasting blood glucose (122.5 mg/dL, SD 61.0) and HbA_{1C} (6.5%, SD 1.0), and a lower C-peptide (0.41 ng/mL, SD 0.48).

Diabetes Related Secondary Complications. Diabetes related secondary complications experienced by the participants are captured prior to their first infusion procedure and at Registry follow-up intervals post their last infusion procedure. It is the goal of the Registry to continue to track the occurrence of these complications across time to determine any trends. At this time in the Registry, follow-up no observations can be made.

Elevated Laboratory Tests. Reports at the 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) were minimal for ALT (2.8%), AST (2.2%), alkaline phosphatase (2.2%) and for total bilirubin (0.5%). There were no reports at this level for total cholesterol and 8 reports (4.5%) for triglycerides. In addition, there were 10 reports (6.0%), of a participant with an increase in their serum creatinine of greater than 0.5 mg/dL of their baseline level.

Serious Adverse Events. Exhibit I presents the adverse event and serious adverse event rate for islet alone transplant recipients in Year 1 post their first islet infusion. Almost 72% of the recipients experienced at least one adverse event in Year 1, while over 47% experienced one or more serious adverse events in this same period. Of the 521 reported adverse events in Year 1 post first infusion, 32.8% were related to the immunosuppression therapy and 26.7% were related to the infusion procedure. Of the 186 reported serious adverse events in Year 1 post first infusion, 29.6% were related to the immunosuppression therapy and 41.9% were related to the islet infusion procedure.

Exhibit I
Summary of Adverse Events and Serious Adverse Events (SAEs) in Year 1
Post First Infusion (Participants, N=203)

	All Adverse Events (Including SAEs)			Serious Adverse Events		
		Related to Immunosuppression Therapy	Related to Infusion Procedure		Related to Immunosuppression Therapy	Related to Infusion Procedure
Number of Events	521	171 (32.8%)	139 (26.7%)	186	55 (29.6%)	78 (41.9%)
Number of Participants with 1 or More Events	146 (71.9%)	84 (41.4%)	75 (36.9%)	96 (47.3%)	35 (17.2%)	48 (23.6%)

A cumulative total of 236 serious adverse events (SAEs) were reported to the Registry. Of these 236 SAEs, 186 of the events (78.8%) were reported during the first year following their first infusion procedure, suggesting that most SAEs occur during this period. Of the 236 SAEs, 41.1% are classified as life threatening and 40.7% required an inpatient hospitalization. Over 33% of the serious adverse events were classified by the reporting CITR investigator as related to the islet infusion procedure and 25.0% related to the immunosuppression therapy. In 2.1% (N=5) of the reports the SAE was related to both the infusion procedure and to the immunosuppression therapy. Approximately 94% of the SAEs resolved with no residual effects.

The most commonly reported serious adverse events included elevated liver function tests (21.2%) (increased aspartate aminotransferase, alanine aminotransferase, and blood alkaline phosphatase), neutropenia (10.6%), procedural related bleeds/portal vein thrombosis (9.7%)

and abdominal pain (5.5%). The 23 procedural-related bleeds consisted of hematoma (N=2), hemorrhage (N=14) and portal vein thrombosis (N=7) during, or immediately subsequent to, an islet infusion procedure. Currently, two recipients are on coumadin for their portal vein thrombosis, but all other procedural-related bleeds have resolved. The rate of reported bleeds ranged from 18.5% in 2003 to 1.6% in 2004.

Reported Deaths. There have been four reports of death to the Registry. The first is 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 evolve and short-term benefits of islet transplantation such as normal or near normal HbA_{1c} levels in the absence of hypoglycemic episodes have been demonstrated by an ever-increasing number of transplant centers. The long-term safety and efficacy profile of islet transplantation and immunosuppression and the effects of islet transplantation on secondary complications are less well understood and are the focus of current research. With continued participation of the existing and new islet transplant programs, CITR expects, through expeditious analyses and Annual Reports, to assist the islet transplant community in the continued development of islet transplantation into a vital therapy for selected patients with T1DM.

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.

