Seventh Annual Report

Prepared by:
CITR Coordinating Center
The EMMES Corporation
Rockville, MD

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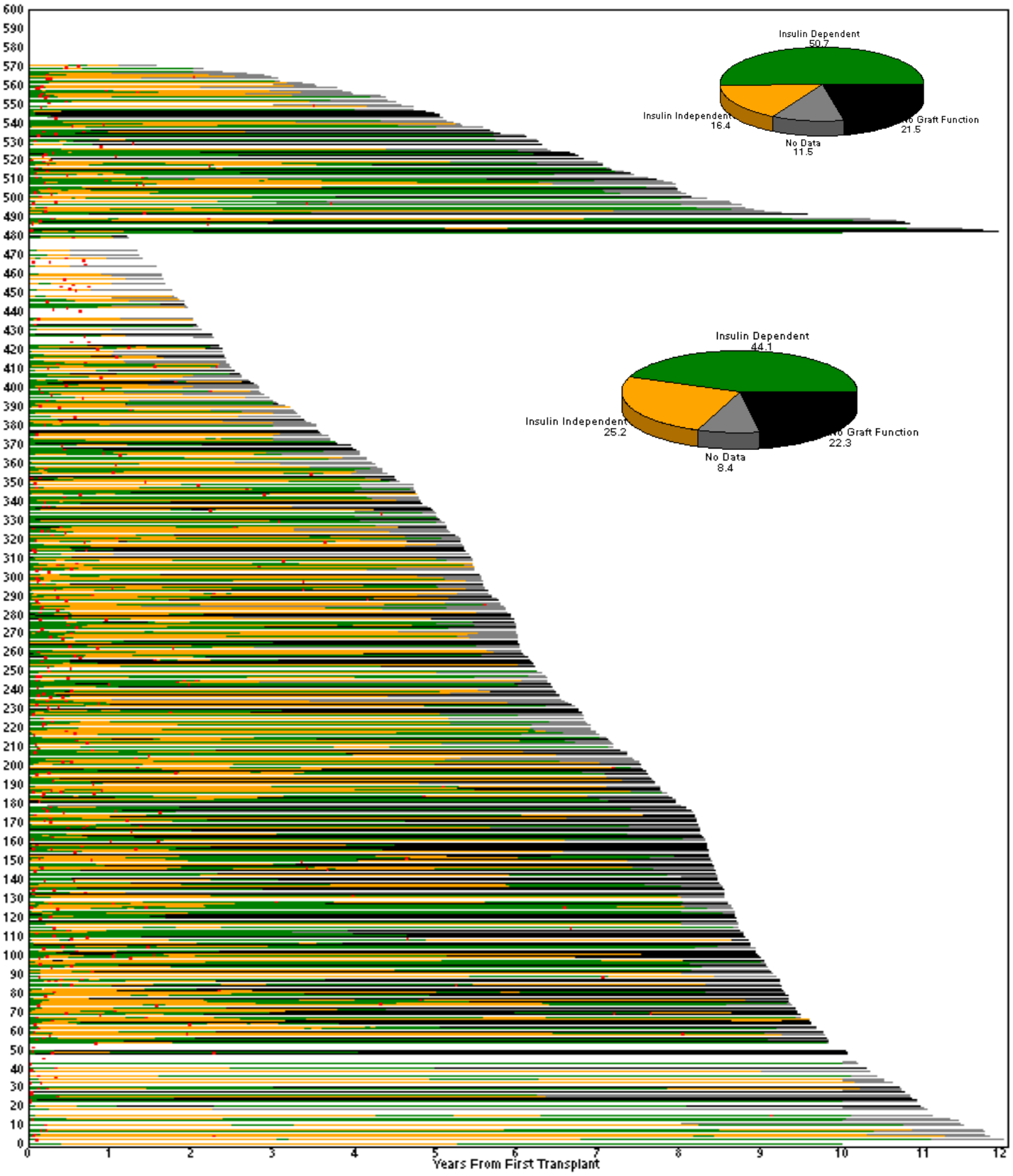

Collaborative Islet Transplant Registry 2010

Follow-up time after initial infusion for each recipient. Top: islet after kidney (N=90), bottom: islet alone (N=481). Yellow: insulin independence; green: insulin-using with graft function (70% average reduction in daily insulin use from baseline); black: no islet function; gray and blank: missing data. Red marks indicate re-infusions. Pie charts show percent of all follow-up time with insulin independence.

COLLABORATIVE ISLET TRANSPLANT REGISTRY
COORDINATING CENTER

December 30, 2011

M E M O R A N D U M

TO: CITR Collaborators, Islet Transplant Centers, Diabetes Research Community, and Interested Public

FROM: Michael Appel, PhD
Director, Islet Biology and Transplantation Research Program
NIDDK

Bernhard Hering, MD
CITR Medical Director &
CITR Scientific Advisory Committee Chair

SUBJECT: 2010 CITR Annual Report

Funded by the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) with supplemental funding from the Juvenile Diabetes Research Foundation (JDRF), the Collaborative Islet Transplant Registry (CITR) serves the mission to expedite progress and promote safety in islet/beta cell transplantation through the collection, analysis, and communication of comprehensive and current data on human-to-human islet/beta cell transplants performed in North America, and Juvenile Diabetes Research Institute-sponsored European and Australian sites.

We are pleased to present this Seventh Annual Report (2010) including data from the great majority of the islet transplant programs active in 1999-2009. We are privileged to have the ongoing collaboration of the United Network for Organ Sharing for the USA donor data, and the past collaboration with United Network for Organ Sharing and the Islet Cell Resource Center Consortium (coordinated by the Administrative and Bioinformatics Coordinating Center, City of Hope, CA), for transplanted islet data for 199-2007. The US Food and Drug Administration and the National Institute of Allergy and Infectious Disease (NIAID) lend continuing support and advice.

The report has been prepared by staff of The EMMES Corporation under the leadership of the CITR Publications and Presentations Committee chaired by Dr. Michael Rickels, and CITR Coordinating Center Principal Investigator, Ms. Franca Benedicty Barton.

We thank everyone who has contributed data and collaborated in the development of the CITR Registry and the production of this Annual Report, including the islet transplant programs and especially the islet recipients who voluntarily consent to the submission of their information. We look forward to their continued participation, along with that of all centers and organizations active in islet transplantation.

NOTICE:

The CITR Annual Report details data received as of March 21, 2011 for all islet transplant recipients transplanted by December 31, 2009.

As exhibited in Chapter 8 Data Quality, an unexpectedly high level of data had not been reported to the CITR Registry for the planned data closure of April 1, 2010. Even after concerted efforts to increase reporting and planning a second data closure in November 2010, the levels of missing data persisted. This severely impacted the planned statistical analyses. The CITR Publications and Presentation Committee recommended that the 2010 Annual report present current information on transplant activity (Chapter 1), recipients and donors (Chapter 2), islet preparations (Chapter 3) and immunosuppression regimens (Chapter 4). Primary and secondary outcomes (Chapter 5) were particularly impacted by under-reporting in the group transplanted since 2007. Hence, Chapter 5 presents data for two eras of recipients: those with first infusion in 1999-2003 (Era 1) and those with first infusion in 2004-2007 (Era 2). Chapters 6 (Laboratory Data) and 7 (Adverse Events) are reported as available for all eras.

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Scientific Summary of the Collaborative Islet Transplant Registry (CITR) 2010 (Seventh) Annual Report

BACKGROUND AND PURPOSE

Pancreatic islets of Langerhans contain insulin producing beta cells that regulate the utilization of dietary sugars by all cells in the body. In persons with Type 1 diabetes mellitus (T1DM), most of the beta cells are destroyed by an autoimmune attack, resulting in the need for pharmaceutical insulin delivered by injection or pump to avoid diabetes-related illness and death. About 5% of the 25.8 million people in the US with diabetes have T1DM, or an estimated 1.5 million people. The only alternatives to daily insulin injections or pump currently available are solid organ pancreas transplant or transplantation of islets of Langerhans isolated from a donated pancreas.

Islet transplantation in the US is experimental and available only at sites that have received exemption from the US Food and Drug Administration (US-FDA) for clinical research of islet transplantation in T1DM. In the US, individual transplant centers may initiate their own independent research protocols or participate in Clinical Islet Transplant Consortium (www.CITIsletStudy.org) to advance the field of islet transplantation. At the Canadian, European and Australian sites, both research and standard of care protocols have been available. Research investigators in clinical islet transplantation and islet science at the various programs contribute data and collaborate on the data analysis to advance knowledge about the risks and benefits of islet transplantation. Each center may publish the results of their local protocols or aggregate experience, and disseminate 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 maintains interactive maps of North American and JDRF European and Australian islet transplant programs at www.citregistry.org.

In 2001, the National Institute of Diabetes & Digestive & Kidney Diseases established the Collaborative Islet Transplant Registry (CITR) to compile data from all islet transplant programs in North America from 1999 to the present. The Juvenile Diabetes Research Foundation (JDRF) granted additional funding to include the participation of JDRF-funded European and Australian centers. The cumulated North American and JDRF European and Australian data are pooled into an annual report. CITR Annual Reports are publically available and can be downloaded or requested in hard copy at www.citregistry.org. This Scientific Summary highlights results from the CITR 2010 (7th) Annual Report, either by direct inclusion or by reference.

PATIENTS AND METHODS

At the time of their first Islet transplant, CITR allograft recipients were 18-67 years of age (mean 45±10SD), had T1DM for 1-61 (28±12) years, and had very poor diabetes control including hypoglycemia unawareness and severe hypoglycemic events. Poor glycemic control can

manifest as frequent episodes of critically low blood sugar levels (which often result as a reaction to injected insulin, requiring the assistance of another person to avert a possibly life-threatening loss of consciousness), wide swings in blood sugar levels (blood glucose lability), or consistently high HbA_{1C} levels (>8% of total hemoglobin).

Data reported to the Registry are abstracted from medical information that is routinely collected by investigators in the course of their research protocols or clinical practice, and for reports to the multiple agencies and entities required by US-FDA regulated trials or according to the requirements of the respective nation.

Detailed follow-up data are abstracted pre-infusion and at Days 7, 75 and 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 Clinical Islet Transplant Consortium (CIT) Terminology Criteria for Adverse Events (TCAE), 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. Additional data have been obtained through data sharing agreements with the United Network for Organ Sharing (UNOS), the Administrative and Bioinformatics Coordinating Center (ABCC, 2001-2009) of the Islet Cell Resource Centers (ICR), and the Data Coordinating Center (DCC) of the Clinical Islet Transplant Consortium (CIT, 2008-).

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.

Statistical analysis. The database for the 7th Annual Report was closed for analysis on March 21, 2011 for data on recipients that were transplanted as of December 31, 2009.

The major focus of the present analyses is to identify factors of patient selection, islet processing and islet transplantation management factors that result in the best possible clinical outcomes of islet transplantation. Reduced data reporting, particularly in long-term follow-up, has posed a challenge for the present analyses. The primary endpoints of insulin use, hence independence or not, and fasting C-peptide levels are the most completely available outcomes data. Monitoring site visits have been performed as scheduled and have included data audits for key recipient baseline and primary outcome data. Additionally, since 2008, site-by-site semi-annual reviews have been conducted by teleconference to maximize reporting of primary endpoints.

Descriptive analyses include tabular or graphical displays of sample means and their standard deviations (SD) or standard errors (SE), and whole-distribution statistics such as median, interquartile range and extremes. Primary outcomes -- analyzed at study time points post first or last infusion -- include percent insulin independent (≥14 consecutive days), C-peptide <0.3 ng/mL, HbA1c <6.5% or drop by ≥2%, fasting blood glucose of 60-140, and severe

hypoglycemic events (Yes/No). First achievement and final loss of insulin independence, as well as complete graft failure, are analyzed by Kaplan-Meier time-to-event analysis with proportional hazards investigation of predictive factors, employing multivariate models to adjust for correlated or confounding factors. Secondary outcomes include whole-distribution description of these and other laboratory measurements, metabolic test results, liver and kidney function measures, and complications of diabetes. Safety is monitored by incidence rates of new adverse events classified by TCAE criteria and related to either infusion procedure or immunosuppression as determined by the local investigator.

Statistical comparisons are observational in nature: reported p-values are not based on controlled, experimental design but on the available data as a sample of convenience. The results should be used to direct future research as well as guide current clinical practice.

RESULTS

Islet Allograft Transplantation Activity 1999-2009. As of December 31, 2009, the CITR Registry included data on 571 allogeneic islet transplant recipients (481 islet transplant alone, ITA) and 90 islet after or simultaneous with kidney (IAK/SIK), who received 1,072 infusions from 1,187 donors. The North American sites contributed 66% and the JDRF European and Australian sites contributed 34% of the recipients. Combining the ITA and IAK/SIK recipients, 31% received a single islet infusion, 47% received two, 20% received three, and 2% received 4-6 infusions.

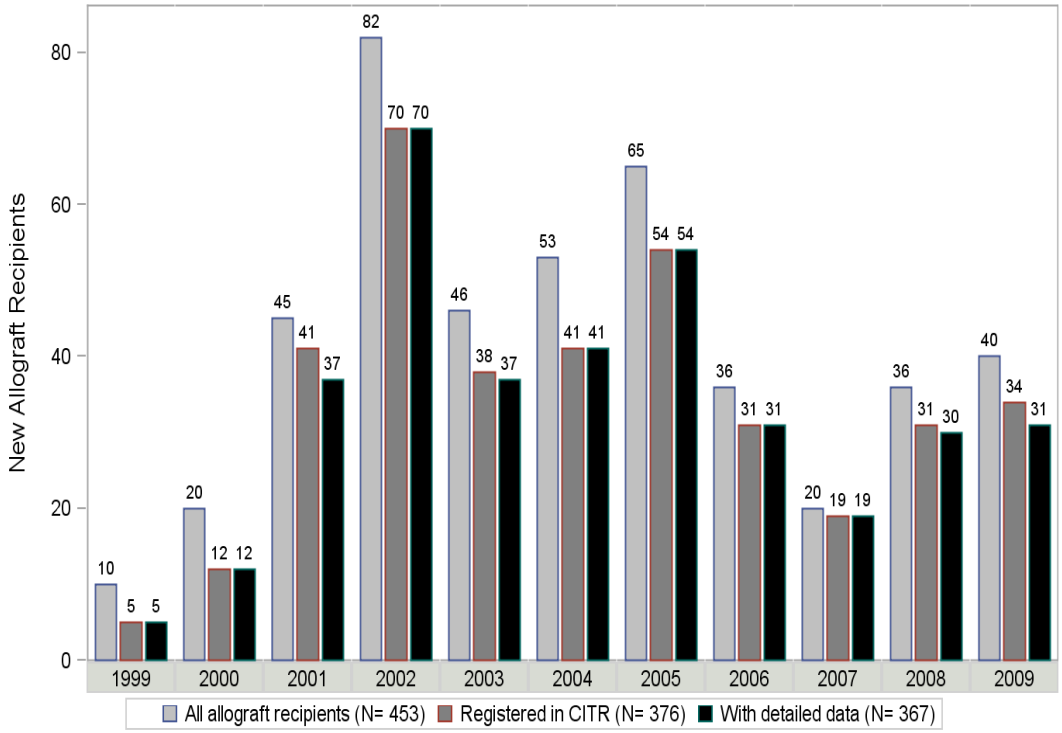
Exhibit A
CITR Recipients, Infusions and Donors by NIDDK/JDRF Sites and by ITA/IAK-SIK
Consented, Registered and First Infused in 1999-2009

	Islet Transplant Alone (ITA)			Islet After Kidney or Simultaneous Islet-Kidney (IAK-SIK)			
	Total	**North America**	**Europe/ Australia**	Total	**North America**	**Europe/ Australia**	**GRAND TOTALS**
Recipients	**481**	341	140	**90**	35	55	**571**
Infusions	**897**	650	247	**175**	66	109	**1,072**
Donors	**988**	693	295	**199**	73	126	**1,187**

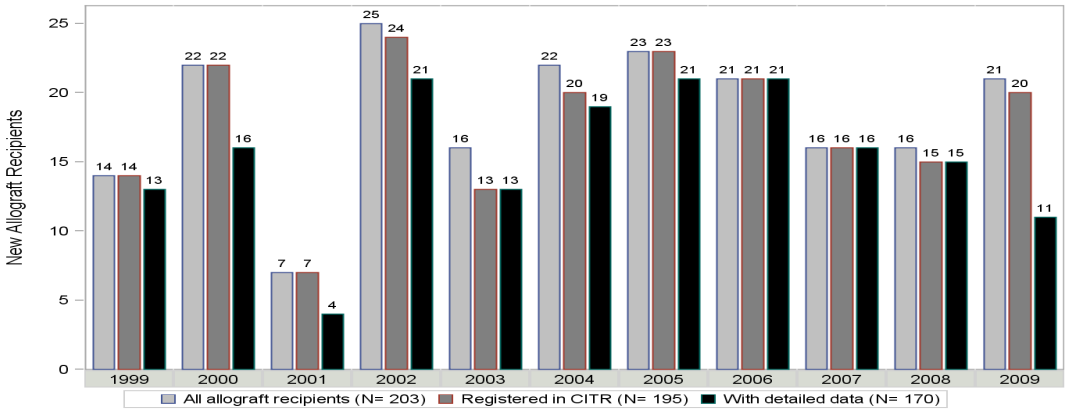
Exhibits B-1 and B-2 display the data collected from the islet transplant programs in North America and the JDRF European and Australian sites from 1999 through 2009. Of the 453 total North American recipients reported by general survey of the sites to have received an islet allograft in 1999-2009, 376 (83%) consented to and were registered in CITR. Detailed data was available on 367 of these recipients, representing 81% of the overall 453. While islet transplantation declined dramatically in 2006-2007 in North America and less so at the JDRF European and Australian sites, it has seen a definite resurgence in 2008-2009, not only in the CIT trials cases but also in local protocols.

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

1. Allograft recipients at CITR North American Centers 1999-2009



2. Allograft recipients at CITR European and Australian JDRF Centers 1999-2009



Islet Transplant Recipient Characteristics. Mean age of islet allograft transplant recipients in CITR has risen over the decade from 42±9 SD to 49±9 years and the mean duration of diabetes has risen from 26±12 to 32±13 years. Mean recipient body mass index (BMI) has remained steady at 23.4±0.1 SE kg/m^2. About 60% of the recipients were female. There has been limited racial and ethnic diversity in islet transplantation. Prior insulin pump use rose from 30% to 45% over the decade while daily insulin requirement dropped from 36.3±1.1 SE to 31.5±1.5. Pre-infusion mean HbA1c has remained steady at 7.8±0.1%, while fasting blood glucose decreased from 199±8.3 to 163±9.3 mg/dL and basal C-peptide fell from 0.3±0.01 SE to 0.1±0.01 ng/mL,

with very few recipients in the recent era (2007-2009) transplanted with a basal C-peptide>0.3 ng/mL. The percent of recipients taking lipid-lowering medications has increased over the eras 1999-2003, 2004-2006 and 2007-2009, from 24% to 47%. About 43% were CMV-positive, and 15% were PRA Class I positive.

Donor Information. All donors were deceased, at a mean age that rose from 42.1±0.5SE to 44.8±0.8 years with mean BMI rising from 28.0±0.3 to 30.3±0.4 over the decade. About 58% of the donors were male, and in North America, <10% were Hispanic and 90% were white. About 47% of the donors had cerebrovascular/stroke cause of death while 25% experienced head trauma. Approximately 36% of the donors had a history of hypertension and 19% had a history of alcohol dependency.

Thirty-two percent (32%) of the donors received a transfusion during their terminal hospitalization, while only 6% received a transfusion intraoperatively. Fifty nine percent (59%) of the donors received steroids and 95% received at least one vasopressor during the terminal hospitalization. Peri-recovery insulin use rose from 32% to 60% over the decade. A total of 10 donors tested positive for anti-HBC, one tested positive for RPR-VDRL and one for HCV. Mean serum creatinine of the donors remained steady at 1.1 mg/dL, while mean maximum stimulated blood glucose decreased from 245±5.9 SE to 214±5.4 mg/dL.

Pancreas Procurement and Processing. Mean time from cross clamp to pancreas recovery was 44±22SD minutes while mean cold ischemia time was 7.3 hours (range 1 to 27). Pancreas preservation with UW-only fell from 56% to 19% while HTK use rose from 0% to 23% and preservation other than UW, 2-layer, HTK, Eurocollins and Celsior rose from 15% to 31% over the decade. For digestion, use of Liberase HI dropped from 86% in 1999-2003 to 6% in 2007-2009, while Serva/NB1 use rose from 1% to 47%, and other collagenase rose from 1% to 13%. Thermolysin use increased from 1% to 13% and pulmozyme use rose from 19% to 45%. Culturing of the islets for >6 hours rose from 29% to 49%, with mean culture time rising from 12±17 SD to 26±19 hours. All of the pancreata processed used a density gradient for islet purification. Of the 1,072 islet preparations, sixteen showed a positive aerobic culture (1.5%), five showed a positive anaerobic culture (0.5%), five showed a positive fungal culture (0.5%), and one tested positive for mycoplasma (0.1%).

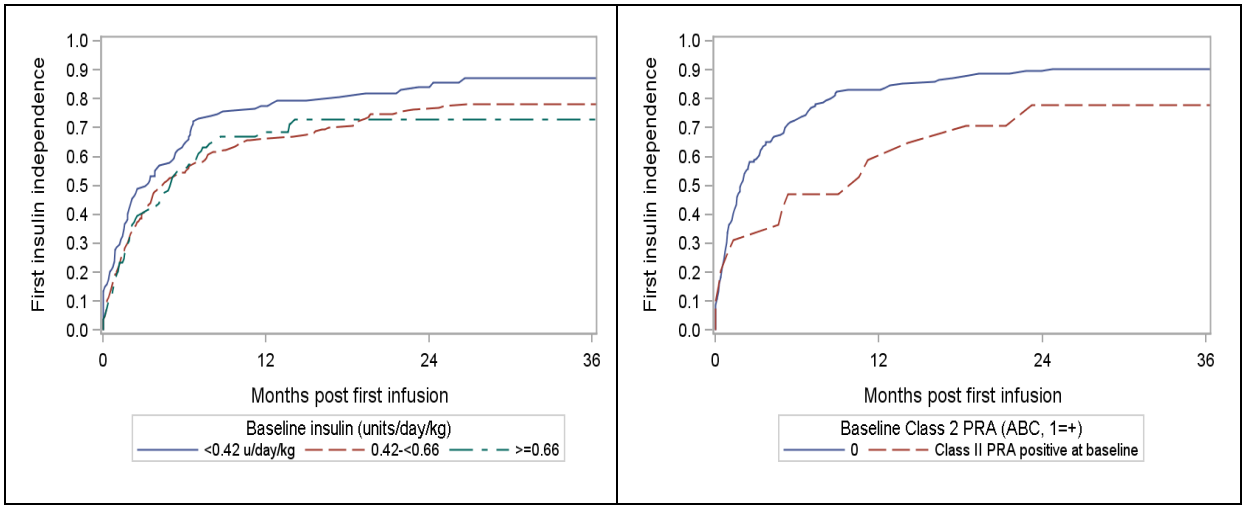
Islet product characteristics. Mean total IEQs infused per infusion rose from 417±7.5SD 1000s to 463±11.2, beta cells rose from 217±17 to 335±32 1000s, endotoxin/kg fell from 0.3±0.001 EU to 0.1±0.001, and total DNA rose from 8.3±0.9 µg to 14.2±1.3.

Immunosuppression Therapy. Induction with IL2R antagonists only, which comprised about 80% of all initial infusions in 1999-2003, was replaced or supplemented with regimens that included T-cell depletion with/without TNF antagonists in over 80% of the infusions performed in 2007-2009. In 1999-2003, maintenance immunosuppression was predominantly (~75%) calcineurin+mTOR inhibitor combinations. It was increasingly replaced or supplemented in 2004-2009 by a calcineurin-inhibitor (CNI) and IMPDH-inhibitor combination, which was also increasingly used in long-term follow-up of early era transplants.

Graft Function. First achievement of insulin independence measured from initial islet infusion (Exhibit C), with or without subsequent infusion, is an indicator of the rate of engraftment under the real-time conditions of competing events including early graft loss, islet resource availability, patient/doctor decisions and myriad other factors, some of which are characterized in the CITR data and others 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. Overall, non-stratified achievement of insulin

independence was 65% in the first year post first infusion (with or without reinfusion), and by Year 2 this increased to 75%. Among the most predictive factors of first achievement of insulin independence were lower baseline insulin requirement and negative Class II PRA (Exhibit C). Multivariate analysis including time-dependent factors such as re-infusion and changes in immunosuppression over time is deferred to a focus topic analysis.

Exhibit C
First Achievement of Insulin Independence
Post First Infusion (Censored at final graft loss or end of follow-up)



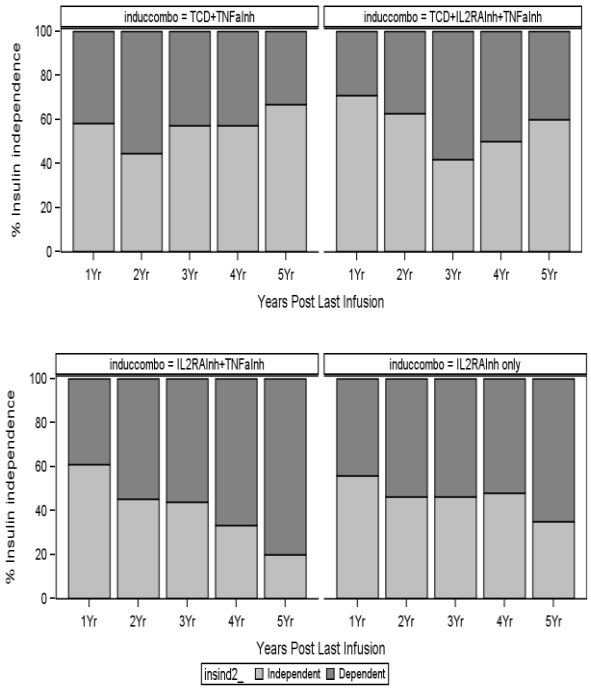
Among factors potentially predictive of successful long-term islet function are induction and maintenance immunosuppression, with 5-year insulin independence rates of 60-70% seen with combinations utilizing T-cell depletion and TNF antagonism compared with IL2RA alone (Exhibit D1, p=0.07), and maintenance combinations that included CNI and IMPDH inhibitors compared with CNI+mTOR inhibitors (Exhibit D2, p=0.02).

Improved insulin independence rates are seen also with older recipient age (p<0.01, Exhibit D3), lower insulin requirements (p=0.004, Exhibit D4), even in this patient population with high rates of hypoglycemia unawareness and severe hypoglycemic events. Additional beneficial factors include higher total IEQs infused over all infusions (p=0.01, Exhibit D5), 2 (but not ≥3) total infusions (p<0.01 Exhibit D6), and lower recipient cholesterol. Beneficial donor factors include age<35 yrs, use of vasopressors and insulin pre-recovery. Beneficial islet recovery and processing factors include HTK preservation, use of pulmozyme and/or thermolysin, and culturing at least 6 hours. The beneficial effect of these factors, including the immunosuppression regimens employed since the 2004-2006 era, is also seen for HbA1c<6.5% or a drop by 2%, and absence of severe hypoglycemic events (see full report). All of the foregoing results are based on univariate analysis.

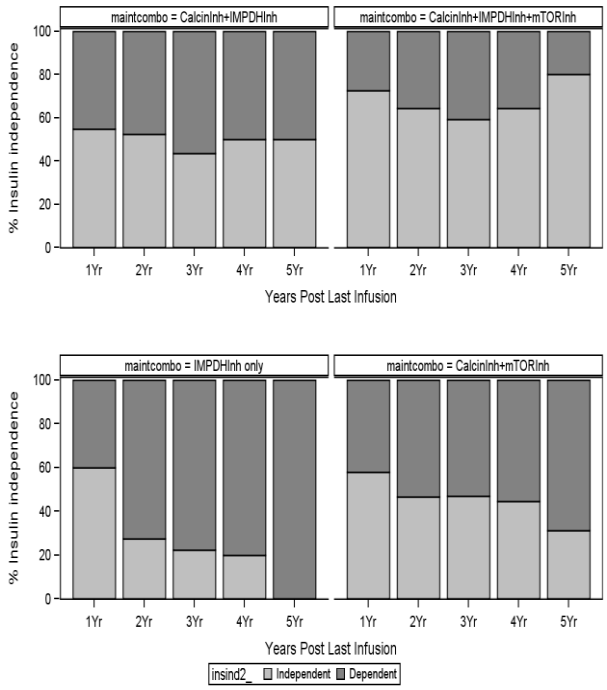
Although sustainability of insulin independence declines over long-term follow-up, the rates of long-term graft function improved over the decade. Recipients transplanted in 2004-2007 retained insulin independence significantly longer than those transplanted in 1999-2003 (p=0.009, see full report). This is only partially accounted for by changes over the decade in the most significant factors associated with long-term benefit (Exhibit D).

Exhibit D
Percent insulin independence post last infusion by predictive factors

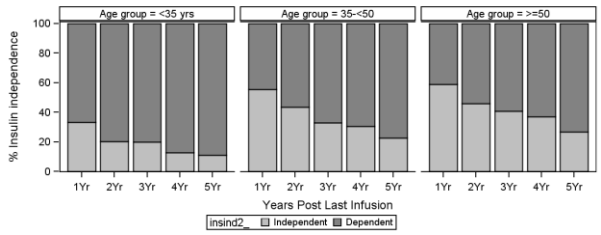
1. By induction immunosuppression combination



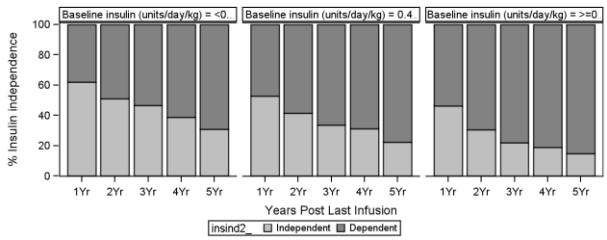
2. By maintenance immunosuppression combination



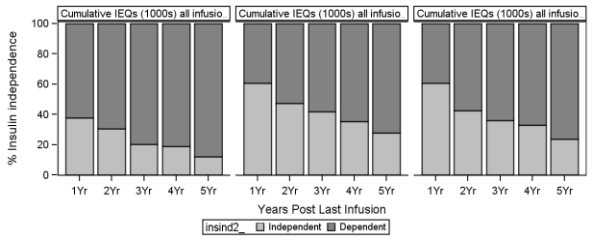
3. By recipient age



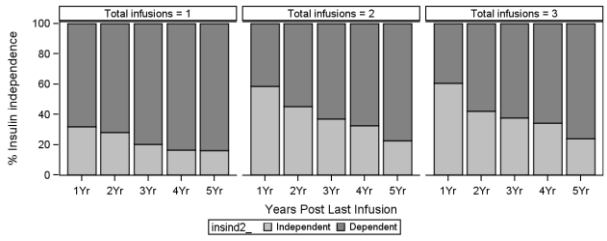
4. By pre-transplant insulin requirement



5. By cumulative IEQs over all infusions

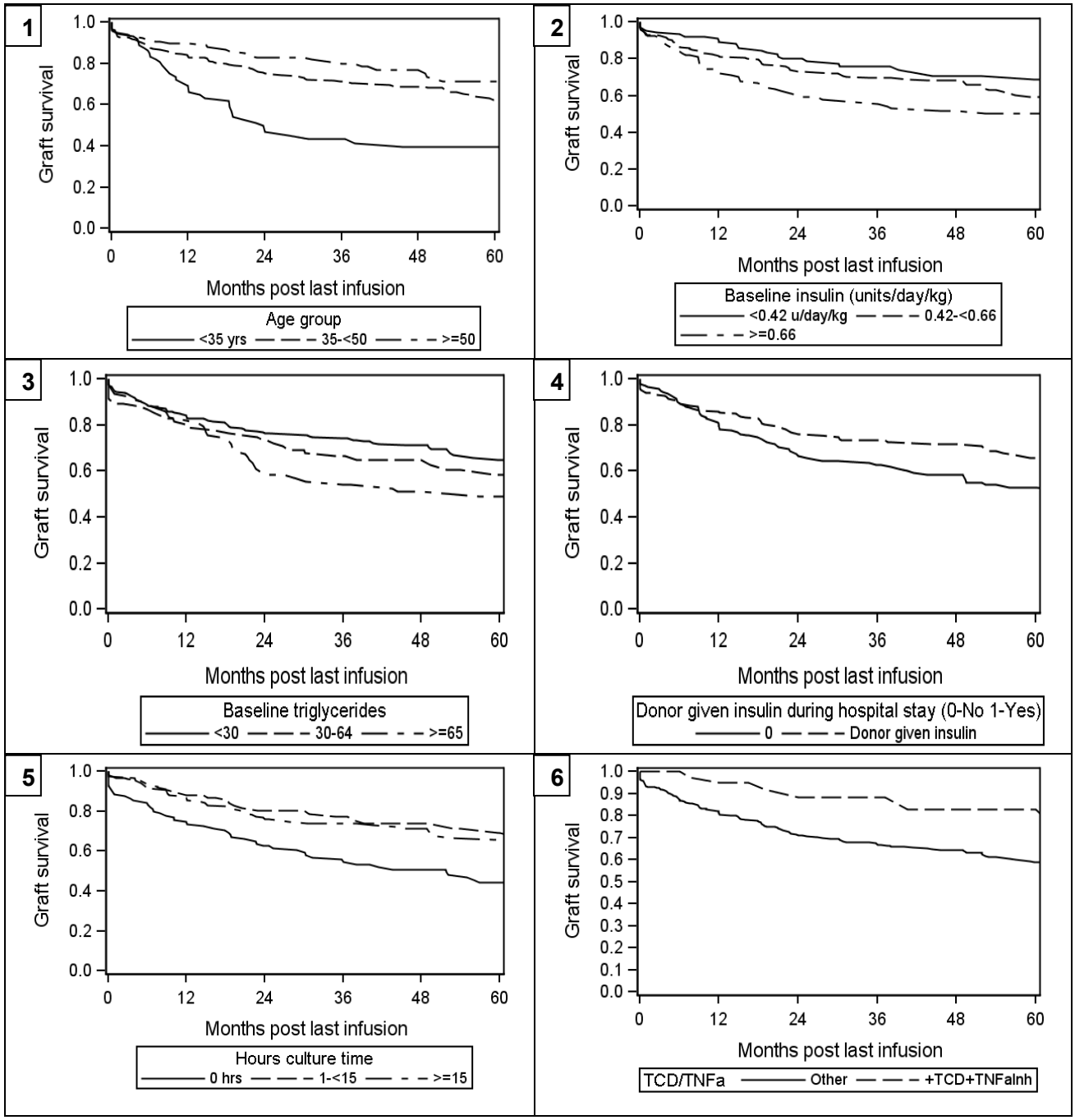


6. By total number of infusions



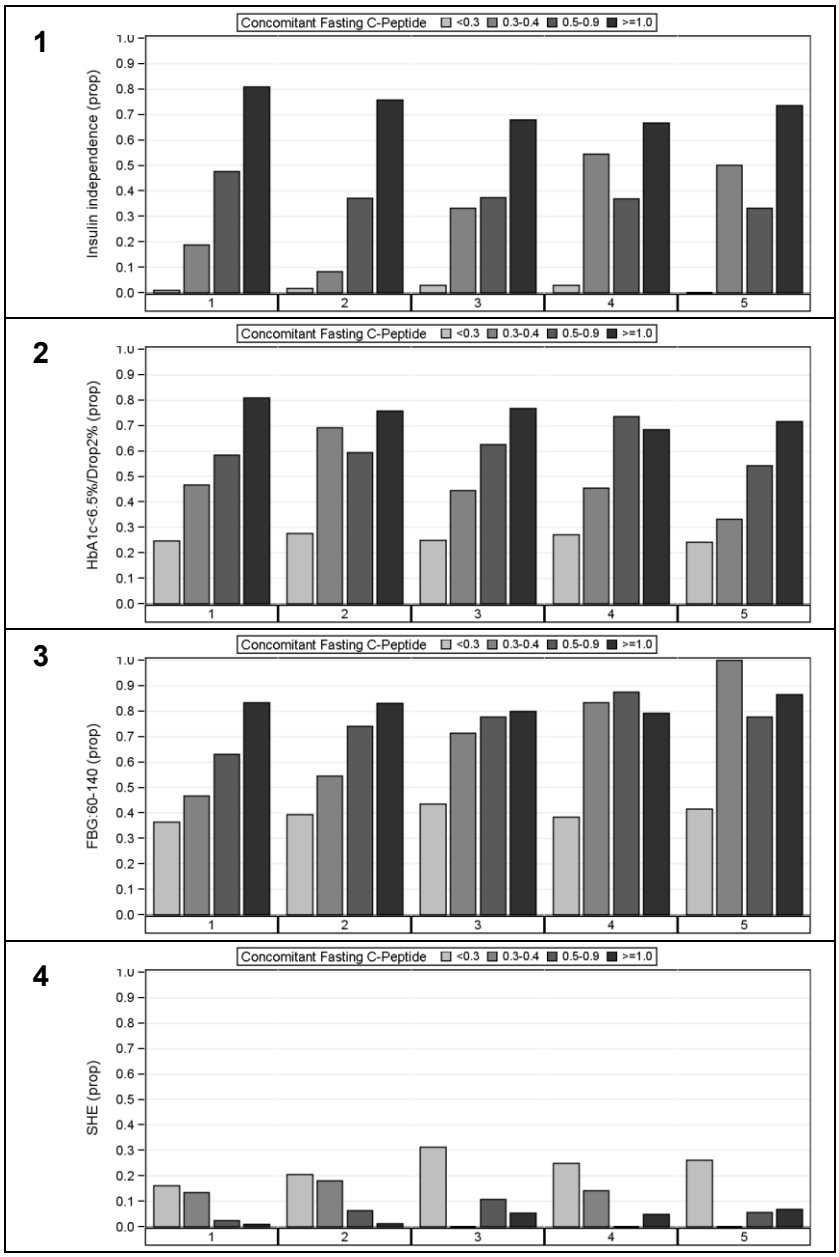
Similarly, graft function is lost over long-term follow-up, although it too varies substantially according to various factors. By Kaplan-Meier and Cox proportional hazards analysis, graft survival (fasting C-peptide≥0.3 ng/mL) can range as low as 40% at 5-years with unfavorable factors (e.g., recipient age <35 years, p<0.001, Exhibit E1), or islets not cultured (p<0.001, Exhibit E4), to upwards of 80% at 5 years with favorable factors (e.g., T-cell depletion plus TNF-a inhibition, p=0.04, Exhibit E6).

Exhibit E
Time to complete graft failure post last infusion



Even partial graft function, i.e., fasting C-peptide of 0.3-0.5 ng/mL usually requiring some level of exogenous insulin use, is associated with improved HbA1c, greater glycemic control, and lower levels of severe hypoglycemia (Exhibit F): the higher the fasting C-peptide level, the higher the likelihood of insulin independence, HbA1c<6.5% or drop by 2%, FBG of 60-140, and the lower the likelihood of severe hypoglycemia. Even with C-peptide<0.3 ng/mL, severe hypoglycemia occurs less than 30% at any follow-up, a substantial reduction from the baseline level of about 70%.

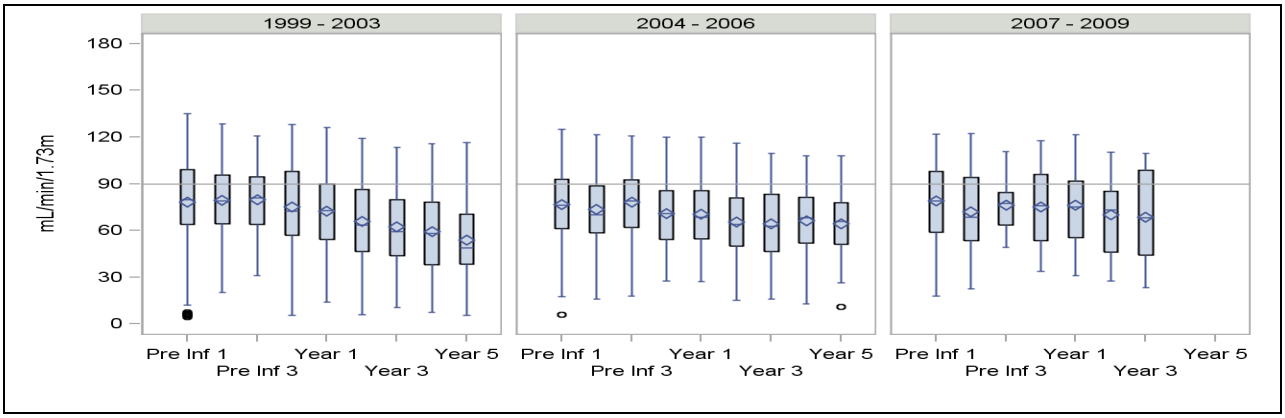
Exhibit F
Insulin independence (1), HbA1c <6.5 or drop by 2% (2), FBG 60-140 (3) and Severe hypoglycemic events (4)
By concurrent C-peptide level, at annual follow-up post last infusion

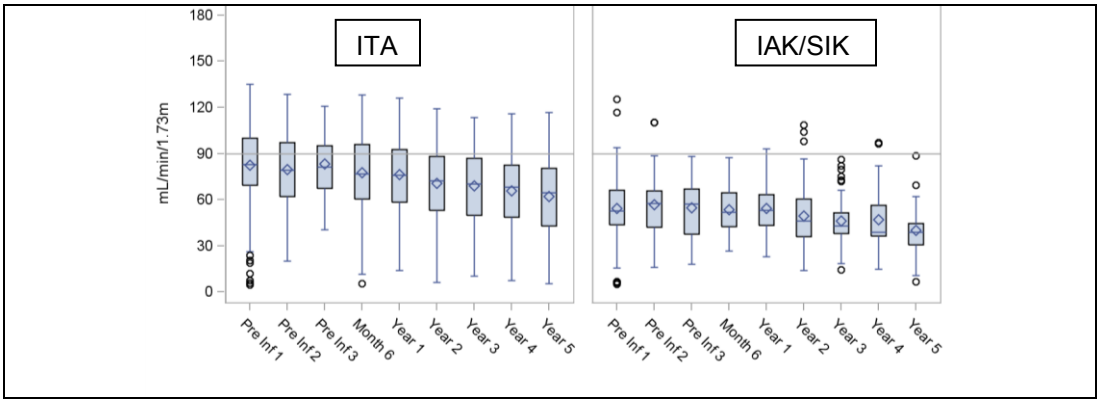


Adverse Effects. The post-transplant increases in ALT and AST levels seen in the early era (1999-2003), followed by return to pre-transplant levels by 1 year, were virtually eliminated in

the most recent era (see full report Exhibits 6-1 & 6-2). The steady rise in serum creatinine over 5 years post transfusion in the early era was also virtually eliminated in the 2004-2006 era (see full report Exhibit 6-9). The decline in CKD-EPI calculated GFR (eGFR) seen in 1999-2003 was less steep in 2004-2006 and 2007-2009 (Exhibit A). Compared with an age-unadjusted cohort of 1,141 T1D followed by the Diabetes Control and Complications Trial and then by the Epidemiology of Diabetes Interventions and Complications (EDIC) (The DCCT/EDIC Research Group, 2011) who started with mean eGFR levels of 126 ml/min/1.73m^3, CITR allograft recipients had much lower mean eGFR (83±24SD for ITA and 54±23 for IAK/SIK) at their first transplant. CITR ITA recipients exhibited a decline in eGFR of 16.5±20.3 and IAK/SIK experienced a mean decline of 7.7±32.6 ml/min/1.73m^3 in 5 years from first infusion, compared to a mean decline of about 9 ml/min/1.73m^3 over the first 5 years in the DCCT.

Exhibit G
Chronic Kidney Disease Collaboration (CKD-EPI) Estimated GFR (mL/min/1.73m2)





Neoplasms. A total of 29 instances of neoplasm have been diagnosed in 27 of the 571 islet recipients who collectively represent a total of about 1,800 person-years of observed follow-up. This equates to about 0.02 neoplasms per person-year. Twenty-one (72%) were classified as benign: 16 instances in 13 patients (1 in 11 patients, 2 in one patient, and 3 in another) of basal or squamous cell carcinoma of the skin; the 11 patients with a single instance recovered completely, and the other two recovered with sequelae. There were 6 instances of malignant ovarian cysts, three instances of breast cancer (once in one patient and twice in another); two instances of lung cancer; and two instances of thyroid cancer. Of the 12 patients developing non-skin cancers, six (50%) recovered completely, 2 recovered with sequelae, 3 did not recover, and 1 died (lung).

Deaths. There have been 18 reports of death to the Registry for islet allograft recipients, for 3% crude mortality over a mean of 6 years elapsed follow-up per patient (including periods after complete graft failure and loss to observed follow-up). Causes of death were (# cases): infection (5); cerebral hemorrhage (3); cardiovascular (2); acute respiratory distress syndrome (1); diabetic ketoacidosis (1); lung carcinoma (1); multi-organ failure of unknown etiology (1); acute toxicity (1); and unknown/unreported causes (3).

CONCLUSIONS

In the years since 2005, fewer North American centers performed islet transplantation, with half as many islet transplant recipients in 2007 as in each year from 2001 to 2005. Notably, both center activity and recipient numbers increased in 2008-2009 compared to 2007. With the continuation of Clinical Islet Transplantation (CIT) Consortium protocols that began in 2008, the number of new islet cell recipients has risen somewhat in North America, and remained steady in Europe and Australia in 2008-2009.

The safety-risk profile indicates that over 1999-2009, recipients of allogeneic islet transplantation were much more impacted by their disease than either of the DCCT-EPIC T1D cohorts, being substantially older, having diabetes for many more years, exhibiting much more impaired kidney function at initial transplant, and suffering from very poor glycemic control marked by frequent episodes of severe hypoglycemia. Despite the burden of immunosuppression, CITR allograft recipients exhibited substantial benefit with acceptable risk as evidenced by low levels of infusion-related complications, and relatively few events of immunosuppression-related cancer and death. Increased cancer risk is associated with both diabetes (Hemkens, et al., 2009; Suh, 2011; Noto, Osame, Sasazuki, and Noda 2010) and solid organ transplantation (Engels, et al., 2011), making it difficult to predict expected rates of neoplasm in T1D islet transplant recipients. Declining kidney function, while of concern, is not comparable to the full DCCT-EPIC cohorts: in CITR allograft recipients, eGFR started much lower relative to the DCCT-EPIC cohorts, declined at higher rates in the ITA group and declined at similar rates in the IAK/SIK group, which were very low to start with.

Islet transplantation continues to show improved long-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. The accumulated experience in islet transplantation indicates that the best candidates for islet transplantation are recipients ≥35 years of age in relatively better glycemic control. The use of vasopressors and insulin in the donor at pre-recovery, as well as use of T-cell depletion with TNF antagonism for induction, and CNI with IMPDH inhibitors for maintenance immunosuppression, are associated with improved outcomes.

Acknowledgments and Disclaimers

The Collaborative Islet Transplant Registry is funded by the National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, USA, and by a supplemental grant from the Juvenile Diabetes Foundation International. Additional data is made available through cooperative agreements with the US United Network for Organ Sharing, Alexandria, VA, and the Administrative and Bioinformatics Coordinating Center of the City of Hope, Duarte, CA (1999-2009). The CITR investigators (roster available at www.citregistry.org) have contributed data used in this report. The principal investigator and biostatisticians of the CITR Coordinating Center (roster available at www.citregistry.org), had full access to all the study data and assume responsibility for the integrity of the data, the accuracy of the data analysis, and the overall results and conclusions presented. Members of the CITR Publications and Presentations Committee over the life of the Registry (roster available at www.citregistry.org) contributed substantially to the analysis of the data and interpretation of the results. No collaborator discloses any conflict of interest in reporting the results presented in the CITR Annual Reports or the Scientific Summary. The voluntary participation of the islet transplant recipients is gratefully acknowledged.

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REFERENCES

The DCCT/EDIC Research Group (2011). Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. *N Engl J Med*, November 12, 2011: Epub ahead of print (10.1056/NEJMoa1111732).

Engels E, Pfeiffer R, Fraumeni J, Jr, Kasiske B, Israni A, Snyder J, Wolfe R … & Lin M (2011). Spectrum of cancer risk among US solid organ transplant recipients. JAMA, 306(17): 1891-1901.

Hemkens L, Grouven U, Bender R, Günster C, Gutschmidt S, Selke G & Sawicki P (2009). Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: A cohort study. *Diabetologia*, 52(9):1732-44. Epub: 2009 Jun 30.

Noto H, Osame K, Sasazuki T & Noda M (2010). Substantially increased risk of cancer in patients with diabetes mellitus: A systematic review and meta-analysis of epidemiologic evidence in Japan. *J Diabetes Complications, 24(5):* 345-353. Epub: 2010 Jul 24.

Suh S & Kim K (2011). Diabetes and cancer: Is diabetes causally related to cancer? *Diabetes Metab J, 35(3)*: 193-8. Epub; 2011Jun 30.

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The Collaborative Islet Transplant Registry (CITR) is sponsored by the National Institute of Diabetes & Digestive & Kidney Diseases and the Juvenile Diabetes Research Foundation. Reprints and additional information may be requested via email to citr@emmes.com or through the CITR website at www.citregistry.org.

Detailed Methods and Definitions

Background and Purpose

Funded by the National Institute of Diabetes & Digestive & Kidney Diseases with a supplemental grant from the Juvenile Diabetes Research Foundation International, the Collaborative Islet Transplant Registry (CITR) expedites progress and promotes 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, and JDRF-sponsored European and Australian centers since 1999. The main vehicle of communicating accumulated results is the CITR Annual Report. This Seventh report summarizing Registry progress through 2010, summarizes information on patients who received one or more islet cell transplants between 1999 and 2009. All CITR Annual Reports are public and can be downloaded or requested in hard copy at www.citregistry.org.

Status and History

This report focuses on **571** islet allograft recipients (**481** islet alone and **90** islet after kidney). Islet autografts are also conducted (over 400 procedures so far in North America) for other indications (principally pancreatitis) and centers may voluntarily report these data also to the Registry. As of December 31, 2009, a total of 163 autologous islet transplant recipients were registered in CITR. Efforts are underway to collect complete autograft information in the Registry.

CITR opened participation to North American centers early in the fall of 2002. The following table summarizes the cumulative numbers of allograft recipients, infusions and donors of the CITR Annual Reports to date.

CITR Annual Report	Allograft Recipients	Allograft Infusions	Allograft Donors
First (2004)	86	158	173
Second (2005)	138	256	266
Third (2006)	227	429	469
Fourth (2007)	292	579	634
Fifth (2008)	325	649	712
Sixth (2009)	412	828	905
Seventh (2010)	**571**	**1,072**	**1,010**

The current report represents a **38% increase in the number of recipients, 12% increase in donors, and a 29% increase in the number of infusion procedures**, compared to last year's report.

Data Sources

CITR implements web-based forms to capture pertinent information necessary to achieve the primary objectives of the Registry and obtain donor, organ procurement, and islet processing data through data sharing agreements with respective organizations (the United Network for Organ Sharing and the Islet Cell Resource Centers). These data characterize and follow trends in safety and efficacy for recipients of islet transplantation, including donor information, islet processing, transplant techniques, and treatment protocols. Data reported to the Registry are abstracted from the medical record routinely collected by the CITR investigators in their care of the transplant recipients, and for scientific evaluations and reports to various agencies 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, Month 12 and annually post each islet infusion for five primary outcomes (insulin use, severe hypoglycemic episodes, hemoglobin A1C, fasting blood glucose and C-peptide). At each new infusion, a new follow-up schedule is established. There is also continuous, event-driven data reporting on vital status, relevant adverse events, non-islet transplant and follow-up, islet graft dysfunction, loss to follow-up, and transfer of the recipient to another islet transplant center. Secondary outcomes include monitoring for specified laboratory surveillance, periodic metabolic testing, concomitant medications and quality of life measures. A copy of the CITR data collection forms may be viewed at the CITR Website (www.citregistry.org).

CITR also collects annual islet transplant activity survey information from all islet allograft transplant centers in North America, regardless of their participation with CITR. All potential islet transplant programs are sent an annual questionnaire requesting the number of islet transplant infusions performed at their islet transplant center as well as the number of recipients.

Study Endpoints

The primary endpoints presented in this report are:

- Insulin independence
- HbA_{1c} level <6.5, 6.5-<7.0 or >=7.0%
- C-peptide $\geq$0.5 ng/mL
- Severe hypoglycemia
- Complete islet graft failure (fasting C-peptide<0.3 ng/mL without recovery or subsequent infusion)

Secondary endpoints include:

- Average daily insulin and percent of baseline insulin
- Fasting plasma glucose
- Laboratory indicators of complications of diabetes and major organ function
- Metabolic testing

These are variously described by prevalence bar charts (frequency distributions) pre-infusion and post first and last infusion, accounting for all participants expected at each time point. For prevalence bar charts, all recipients expected at each follow-up time point based on the dates of their infusions and the report cut-off date are included in the analysis. Bar charts are intended

to display prevalence and generally represent 100% of data expected at each time point. Event analysis of incidence and persistence of specified endpoints (e.g., achievement and retention of insulin independence) are analyzed by Kaplan-Meier time-to-event or survival estimates and by Cox proportional hazards regression using relevant baseline factors as stratifying or adjusting covariates.

Insulin use, and dose if used, are available from patient-reported daily diaries post each infusion as well as at pre-specified study time points. Prevalence of insulin independence at each follow-up time point is shown in addition to achievement and loss, because this endpoint in particular can "come and go". A change from insulin dependence to independence by definition requires at least 14 consecutive days of no insulin use. A change from insulin independence to insulin dependence by definition requires a minimum of 14 consecutive days of insulin use. Average daily insulin use is recorded for periods of insulin use before and after any re-infusion procedures, changes in islet graft function, and all scheduled CITR follow-up visits.

Despite the possible transitioning back and forth from insulin dependence to independence, the initial achievement of insulin independence and the final loss are clinically meaningful events that can be analyzed as event-based outcomes with Kaplan-Meier and proportional hazards analysis.

Complete islet failure (CIF) or complete graft loss (CGL) is a reportable event. In addition, C-peptide data was used to impute CIF: any recipient with fasting C-peptides less than 0.3 ng/ml or less than local detectable levels for two consecutive scheduled follow-up visits and no simultaneous stress C-peptide >0.3 ng/mL was imputed as a complete islet failure for this report.

Boxplots used in the report display the distribution of specified continuous measures, e.g., laboratory results. The mean is indicated by a symbol, along with the median (50th percentile, center line of the box), the 25th percentile (lower line of box), and the 75th percentile (upper line of box). Whiskers extend to 2.5 X interquartile range, and outliers are plotted with individual symbols.

Statistical significance of univariate analyses not adjusted for repeated testing or other covariates, is shown for a number of the Exhibits. These are considered observed, nominal p-values outside of any pre-planned Type I error structure. In drawing any conclusions, readers should be mindful that the significance levels control for random variance, but not systematic biases in the data nor multiple testing. It may be that nominal statistical significance of the analyses in other CITR Annual Reports are based on a different sample sizes and will vary from this year's report. However, these analyses do provide insight and direction for future questions and analyses.

Statistical Modeling

The Cox regressions represent a first attempt to comprehensively assess factors that may be predictive of the primary outcomes. Univariate models are used to identify possible effects first. Any factor with an association at a nominal significance level of $p<0.10$ was included in a multivariate model. Multivariate modeling was performed first in a step-down manner, and then manually replicated by stepping up to check for stability of the model. Two or more factors significantly associated with an outcome at $p<0.10$ but also strongly correlated with each other (Pearson $r>0.4$), were stepped into the multivariate model individually to test their effect. Of such correlated factors, the one with the greater effect was retained in the final model. The results of these models should be viewed as preliminary due to the relatively large number of factors, the effect of outliers and highly skewed distributions for many of the factors, and the associations among the factors.

The CITR data are analyzed to characterize the possible outcomes or states that an individual can experience following islet cell transplantation. Such analyses may help elucidate both biological factors affecting outcomes and clinically meaningful predictors of achievement and durability of success. Figure 1 presents one view of the possible states following the first of one to several infusions: individuals can have immediate islet cell failure (primary non function), or they can enter either the insulin dependent or insulin independent states. An individual may change from one state to another before re-infusion: if insulin independence is achieved, it might be lost; other than primary non-function, islet failure can subsequently occur; finally, a subsequent infusion can be performed. Time-to-event models can be used to investigate the effect of pre-infusion patient, donor and islet characteristics on these outcomes after first infusion.

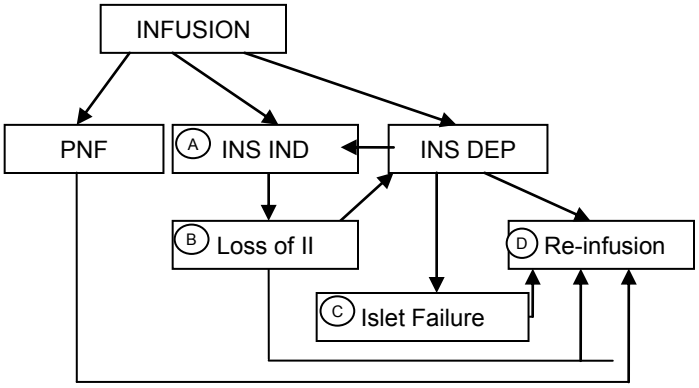


Figure1. Possible states post first infusion (PNF=Primary non-function; INS IND, II=Insulin Independent; INS DEP=Insulin Dependent).

In Chapter 5, we present proportional hazard regression analyses of factors affecting transition to insulin independence and loss of the insulin independent state. Because the insulin dependent state is substantially the complement of the independent state, it is not modeled separately. Because of low event numbers, primary non-function is not analyzed. The absorbing state of death has occurred too infrequently to be analyzed separately; further follow-up and/or a larger sample size will be required before its inclusion would be meaningful. Initial analysis of the transition to the islet failure state is provided. This continues to be analyzed in each Annual Report with more extensive follow-up. There are multiple paths leading to reinfusion; factors affecting this decision include site treatment plans which may not depend on the individual's

paths or outcome states. Analysis of this outcome state is done by logistic regression, as time to event is clinically meaningless.

Following reinfusion, the outcomes path could be extended to depict the identical outcome states following the second and subsequent infusions. Rather than attempting to examine outcomes after each infusion, we consider the experience following a series of infusions as described in Figure 2.

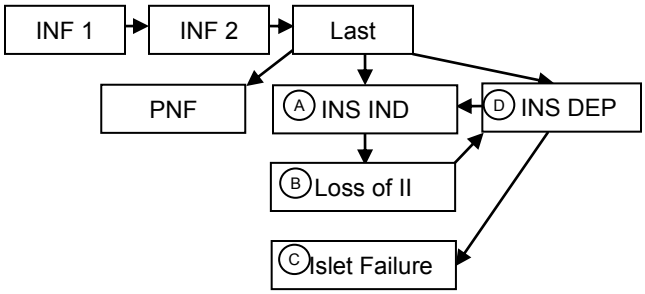


Figure 2. Possible states post last infusion (PNF=Primary non-function; INS IND, II=Insulin Independent; INS DEP=Insulin Dependent).

We call these analyses "post last infusion," defined as all infusions performed in a recipient with at least 6 months follow-up available post last infusion and excluding primary non-function. Only those recipients meeting this definition are included in this analysis. In this view, the outcomes after each infusion are regarded as intermediary steps with focused consideration of the outcome states post last infusion. Chapter 5 also presents univariate analyses of the insulin independence, loss of insulin independence and islet failure states post last infusion, as well as multivariate results.

Limitations and Disclaimers

Data contained in this report must be interpreted cautiously. Even with the combined efforts of the participating centers, the total number of islet transplant recipients remains small. As with any registry, a number of potential biases may exist. First, not all active islet transplant centers in North America or the JDRF sites have submitted data to CITR. Second, not all of the islet transplant recipients or all of the infusion procedures have been reported. Third, some information, especially on follow-up after two years of follow-up, may be reported selectively based on the center's protocol or other local decisions.

No center-specific information is presented in this report.

Data Quality Assurance and Closure

CITR adheres to strict quality control and assurance procedures. All data submitted are reviewed through several quality review processes. Islet transplant recipient data for this report reflect data entered by the islet transplant centers on participants from **January 1, 1999 through December 31, 2009.** These data were reviewed by the Coordinating Center for quality assurance, errors and data outliers. Any missing follow-up information on these participants

were identified and conveyed back to the center for verification and correction. Any questions concerning specific data elements were also sent to the islet transplant centers for review and correction, if necessary. All islet transplant centers were provided ample time for completing any identified data discrepancies. **The database was then updated and closed for analysis on March 21, 2011 based on the recipients that had been registered for CITR at the December 31, 2009 participant registration closure date.**

All participating North American islet transplant centers and the data they submit to the Registry are monitored and audited by the Registry's Coordinating Center. The schedule for monitoring includes an initial visit to the islet transplant center after the first three participants are submitted to the Registry, and then after every 10 participants are entered or at the discretion of the Coordinating Center if less than 10 new participants have been registered. Monitoring reports, with suggestions for improvement, data discrepancies, and all action items are sent both to the islet transplant center and CITR's sponsor, NIDDK.

Definitions

Several key terms used by CITR in the Annual Report exhibits are listed below with their respective CITR definitions:

Abnormal tests: Liver function and lipid tests were analyzed as $\geq$ 1 times the upper limit of normal (ULN) and at $\geq$ 2 times the ULN. The ULN (Stedman's Medical Dictionary, 26th edition, Williams & Williams) for each of the tests are defined as the following:

ALT (alanine aminotransferase):	*56 IU/L*
AST (asparate aminotransferase):	*40 IU/L*
Alkaline phosphatase:	*90 IU/L*
Total bilirubin:	*1.3 mg/dL*
Total cholesterol:	*240 mg/dL*
Triglycerides:	*150 mg/dL*

Adverse Event: Grade 3-5 as classified by the Clinical Islet Transplantation Consortium (CIT), Terminology Criteria for Adverse Events (TCAE), Version 4.0. Adverse event relationships to the infusion procedure and to the immunosuppression regimen are determined by the local CITR Investigator.

Cell volume: Total volume of islet cells in a preparation. Either packed cell volume or settled cell volume may be reported depending on the methods used by the transplant center.

Complete islet graft failure (IGF): Reported by transplant centers when a recipient no longer has detectable C-peptide. However, C-peptide data at scheduled follow-up was used to correct for missing or tardy reports: any recipient with fasting C-peptide less than local detectable levels and stimulated C-peptide less than 0.3 ng/mL (or less than local detectable levels) at their last scheduled follow-up were imputed as a complete islet graft failure for this report.

Complete graft loss (CGL): Synonymous with "complete islet graft failure."

Detectible C-peptide: A C-peptide level greater than or equal to the local laboratory's lower limit of detectability, which may vary in numerical value from one center to another.

Duration of cold ischemia: Duration of time from when the pancreas was placed in cold preservation solution until the heating up of the organ to start the digestion process.

Hazard Ratios: In Cox proportional hazards regression, relative hazard less than 1.0 indicate a reduced risk of the outcome with higher levels of the predictor, and HR greater than 1.0 indicate increased risk of the outcome with higher levels of the predictor. Binary factors are coded 0=no/absent and 1=yes/present.

Hypoglycemia status: Hypoglycemia status at baseline and during follow-up visits is determined by choosing one of the following categories that best describes the participant:

No occurrence: Participant was not diagnosed with hypoglycemia and/or signs and symptoms did not occur.

Having episodes and aware: Participant experiences episodes and has autonomic warning symptoms.

Partial awareness: Participant has a decreased magnitude of autonomic symptoms or an elevated threshold for autonomic symptoms at low glucose levels.

Unawareness: Participant has a lack of autonomic warning symptoms at a glucose level of < 54 mg/dL.

Insulin dependence: Insulin administered for a period of 14 or more consecutive days.

Insulin independence: Free from insulin use for 14 or more consecutive days.

Islet after kidney recipient/simultaneous islet-kidney (IAK/SIK): A recipient of an islet cell transplant with prior or simultaneous kidney transplantation.

Islet alone recipient (ITA): A recipient of an islet transplant with no prior or simultaneous kidney transplantation.

Islet equivalent count (IEQ): Number of islets in a preparation adjusted for size of the islet. One IEQ is equal to a single islet of 150 μm in diameter.

Islet function: Fasting C-peptide detectable by local assay or stimulated C-peptide greater than 0.3 ng/mL.

Islet graft dysfunction:

In *insulin independent recipients* (after completion of induction immunotherapy), islet graft dysfunction is defined as when the recipient displays, with no evidence of infection or drug toxicity, 3 blood glucose readings 2 hours or longer post prandial over 180 mg/dL in any 1-week period OR 3 pre-prandial blood glucose readings over 140 mg/dL in any 1-week period.

In *insulin dependent recipients* (after completion of induction immunotherapy), islet graft dysfunction will be suspected if the recipient displays, with no evidence of infection or drug toxicity, a 50% increase in insulin requirements (with a minimum increase of 5 units per day) OR an increase of 10 units per day over a 1-2 week period.

Islet particle count: Number of islets in a preparation without any adjustment for the size of the islet.

Loss of insulin independence: Time from attainment of insulin independence to the first day insulin was required for 14 or more consecutive days.

Lost to follow-up: Site has submitted form denoting recipient as having discontinued follow-up voluntarily or without reason.

Missing: Form not submitted on time or item left blank. Clinical site is still required to report a valid value or designate that the answer is unknown.

Outcome of islet graft dysfunction: If a complete dysfunction was not experienced (islet graft failure), there may be:

Partial recovery: Recovery achieved but not to the functional level (as assessed by glycemic control, C-peptide level, and/or insulin requirements) prior to the change in islet graft function.

Full recovery: Recipient was able to obtain the same level of functioning (as assessed by glycemic control, C-peptide level, and/or insulin requirements) prior to the change in islet graft function.

PRA: Panel Reactive Antibody is a blood test that measures anti-human antibodies. The PRA score represents the percentage of the population that react with the anti-human antibodies in the blood

Serious Adverse Event: Any adverse event involving death, life threatening event, inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or required intervention to prevent permanent damage, regardless of the TCAE grading. Serious adverse event relationships to the infusion procedure and to the immunosuppression regimen are determined by the local CITR Investigator.

Severe hypoglycemia: Having hypoglycemic events requiring the assistance of another person to diagnose symptoms or administer treatment. Prior to the first infusion, this is defined as the number of episodes in one year prior to infusion. At follow-up, it is defined as the number of episodes during the follow-up period (0 to 30 days post infusion, 30

days to 6 months post infusion, 6 to 12 months post infusion, or at yearly intervals thereafter).

Unknown: The value or response to a form item is not available from the medical record, the recipient, or from any other source data. Distinguished from “missing” which means not answered/left blank.

Chapter 1
Islet Transplant Activity

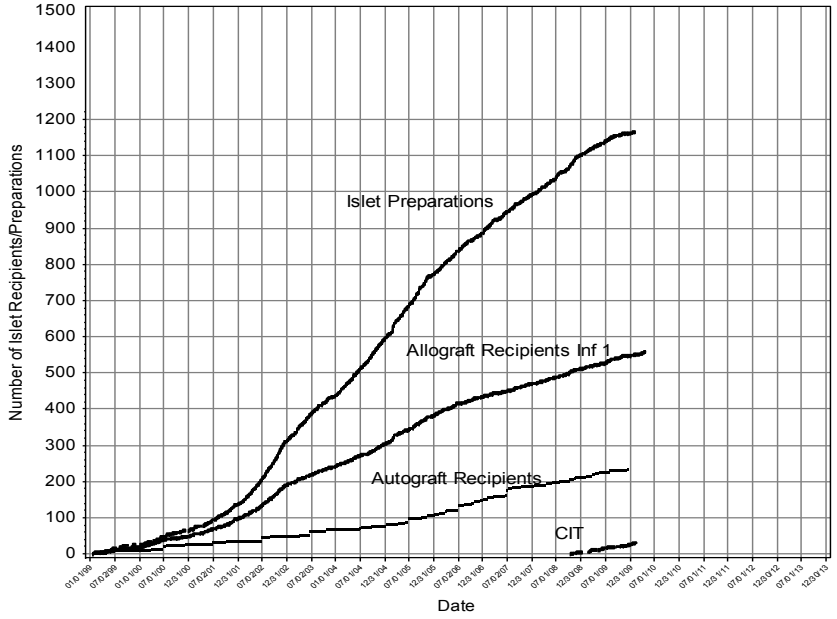
Islet Transplant Activity

From 1999 through 2009, 27 National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) sponsored North American and 5 Juvenile Diabetes Research Foundation (JDRF) sponsored European and Australian islet transplant centers (32 total) contributed data to the Collaborative Islet Transplant Registry (CITR). These sites registered 481 islet transplant alone (ITA) and 90 islet after kidney or simultaneous islet-kidney (IAK/SIK) allograft recipients consenting to have their data reported to the Registry, for a total of 571 allogeneic, human-to-human islet transplant recipients. Another six North American sites transplanted 45 allogeneic islet recipients, of which 38 were transplanted before 2007. Of these six sites, two are still actively transplanting. In 2009, eleven North American sites performed allogeneic islet transplantation, of which 10 participated in CITR. Exhibit 1-1A and 1-1B summarize the total allograft recipients, donors and infusions included in this report.

In 2008, the Consortium for Islet Transplantation (CIT; http://www.citisletstudy.org/) began enrolling islet transplant patients, with CIT enrollment actively ongoing at this writing. All of the CIT sites participate in CITR. Under collaborative agreements stipulated by the common sponsor, the NIDDK of the US NIH, CITR-required data is transmitted to CITR for CITR-consenting patients. Most CIT sites offer both CIT and non-CIT islet transplant protocols.

Exhibit 1-1A
CITR Recipients, Infusions and Donors by NIDDK/JDRF Sites and by ITA/IAK/SIK
Consented, Registered and First Infused in 1999-2009

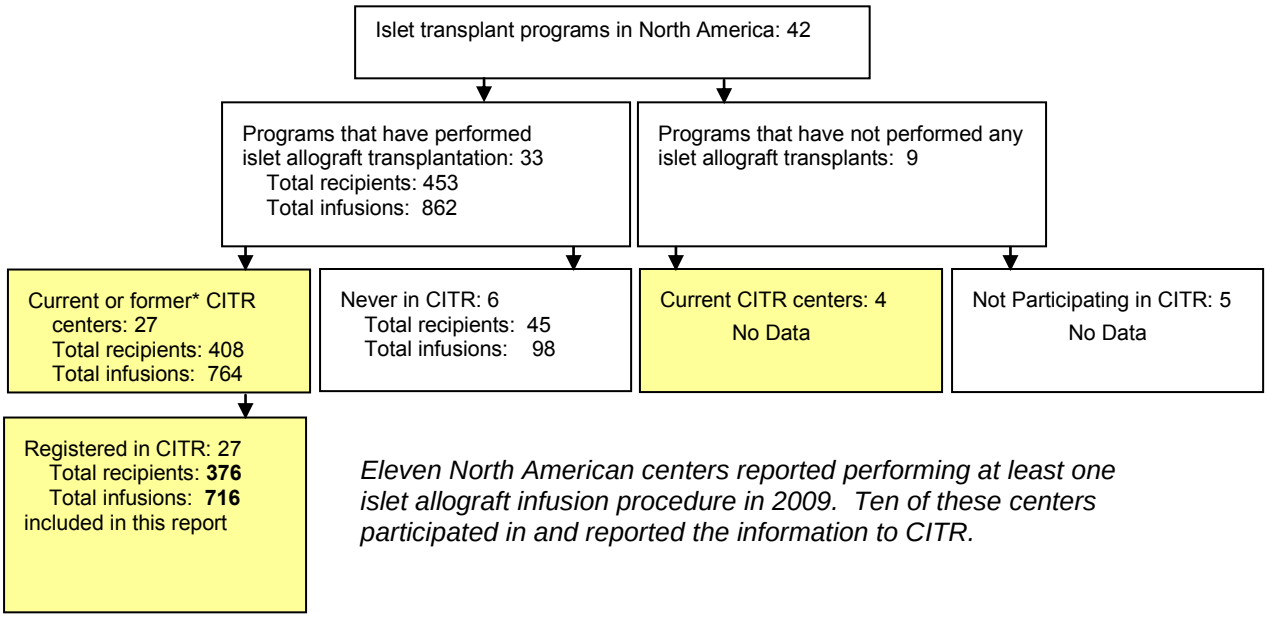
	Islet Transplant Alone (ITA)			Islet After Kidney or Simultaneous Islet-Kidney (IAK/SIK)			
	Total	**North America**	**Europe/ Australia**	**Total**	**North America**	**Europe/ Australia**	**GRAND TOTALS**
Recipients	**481**	341	140	**90**	35	55	**571**
Infusions	**897**	650	247	**175**	66	109	**1,072**
Donors	**988**	693	295	**199**	73	126	**1,187**



NORTH AMERICAN CENTERS

In addition to the data collection for registered islet transplant recipients, CITR conducts an on-going survey, updated at least annually, to identify active islet transplant centers and ascertain the total number of recipients and islet infusions conducted in North America. The following diagram shows the number of centers, recipients and infusions identified and captured by CITR. Overall, 376 of 453 allograft recipients (83%) and 716 of 862 (83%) of all allograft infusions performed in North America are included in this year's Annual Report.

North American Islet Allograft Transplant Centers, Recipients and Infusions Total Performed and Total *Reported* to CITR 1999-2009



Eleven North American centers reported performing at least one islet allograft infusion procedure in 2009. Ten of these centers participated in and reported the information to CITR.

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

Exhibit 1-2A maps the geographic locations of all current and former CITR-participating North American centers. A listing of CITR-participating centers and their clinical personnel is found in Appendix A.

Exhibit 1-3 displays the number of North American centers conducting allograft transplants and of those, the number of centers contributing to this report, by year.

Exhibits 1-4 and 1-5A display the number of allograft recipients and allograft infusions performed in all of North America, and the respective numbers contained in this report, by year.

Overall, there was a steady increase in the number of islet transplant programs joining CITR up to 2005, followed by a decline in centers performing islet transplantation in 2006-2007, then a resurgence starting in 2008.

JDRF CENTERS

Three European (Exhibit 1-2B) and two Australian (Exhibit 1-2C) JDRF centers have contributed detailed data to the Registry. Overall, 195 of 203 (96%) allograft recipients and 356 of 380 (94%) allograft infusions performed between 1999 and 2009 at these five centers are included in this year's Annual Report.

Exhibits 1-4B and 1-5B display the numbers of allograft recipients and allograft infusions performed in the JDRF European and Australian sites, by year.

Infusions

A summary of the total 1,072 North American and JDRF islet allograft infusions by year of infusion is included in Exhibit 1-5. These infusions derived from 1,187 total donors: 931 were single donor preparations, 91 were multiple donor preparations, and the remainder pending.

One hundred seventy-eight recipients (31%) have received a single islet infusion at the time of this report, 268 (47%) received a total of two infusions, 115 (20%) received three infusions, and ten recipients (2%) received a total of four to six islet infusions (Exhibit 1-7).

Of the 571 islet allograft recipients presented in this report, 481 (84%) are islet alone recipients, and 90 (16%) are islet after kidney recipients (Exhibit 1-9). Seven islet alone recipients later received a pancreas transplant subsequent to their islet graft failure.

CITR Allografts Overall

There has been a 39% increase in the number of allograft recipients reported to the Registry since the last Annual Report, as well as a 29% increase in the total number of islet allograft infusion procedures reported.

Autografts

One hundred forty-three (143) North American and 20 JDRF autograft consenting recipients have been registered in the Registry. Detailed data for these recipients is being collected. When complete data are available, a supplemental Annual Report will present analyses for autologous islet transplants.

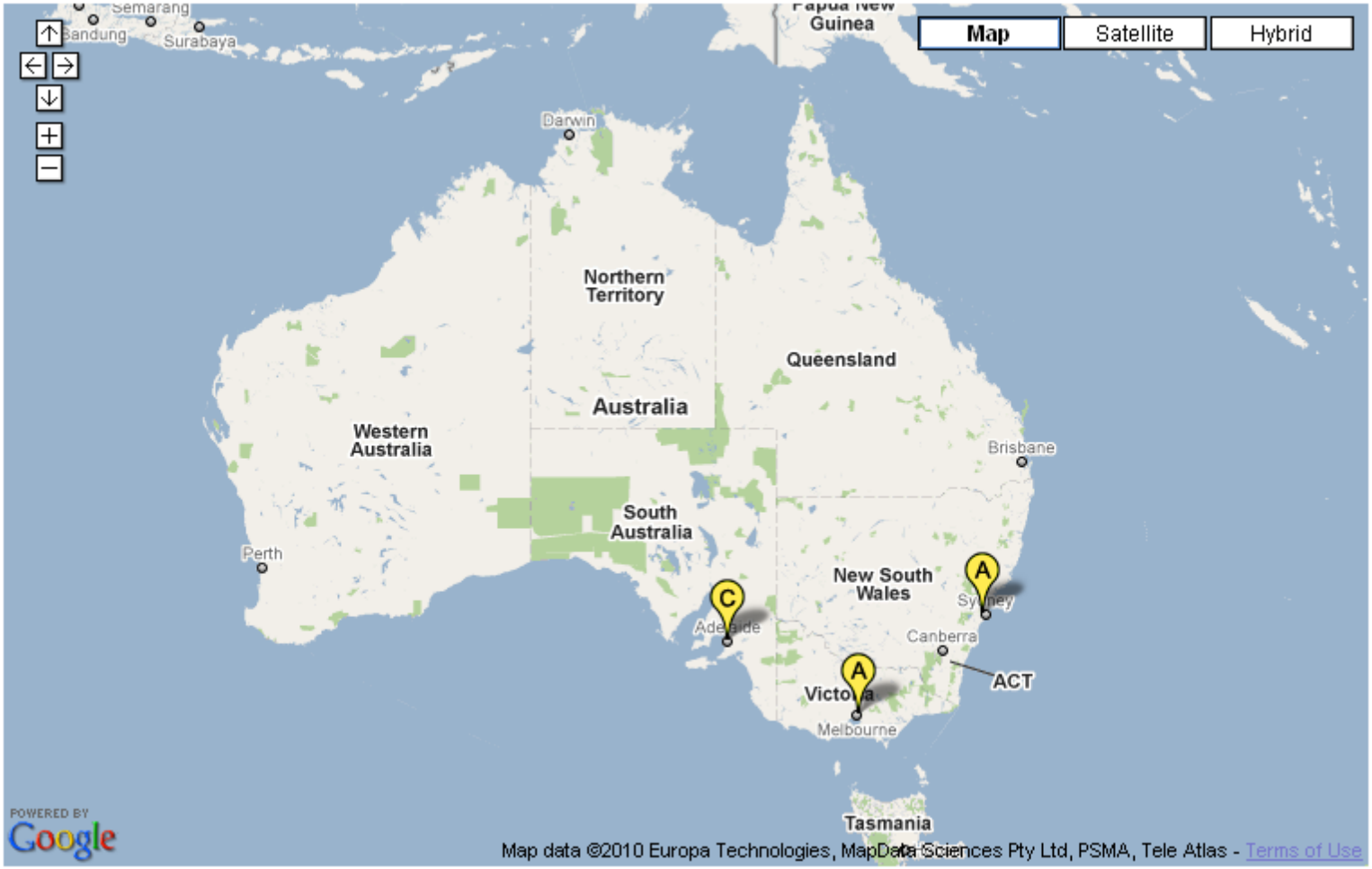
Exhibit 1 – 2A
Islet Transplant Centers Reporting Data to CITR
Participating North American Centers 1999-2009

A - CITR Centers with at least one islet allograft infusion procedure or recruiting in 2009 (N=11)
C - CITR Centers with no islet allograft infusions in 2009 (N=21; three of which have never performed an islet transplant)
D - CITR Coordinating Center
For more information on North American islet transplant programs, please visit the CITR Website at www.CITRegistry.org.

Exhibit 1 – 2B
Islet Transplant Centers Reporting Data to CITR
Participating European Centers 1999-2009

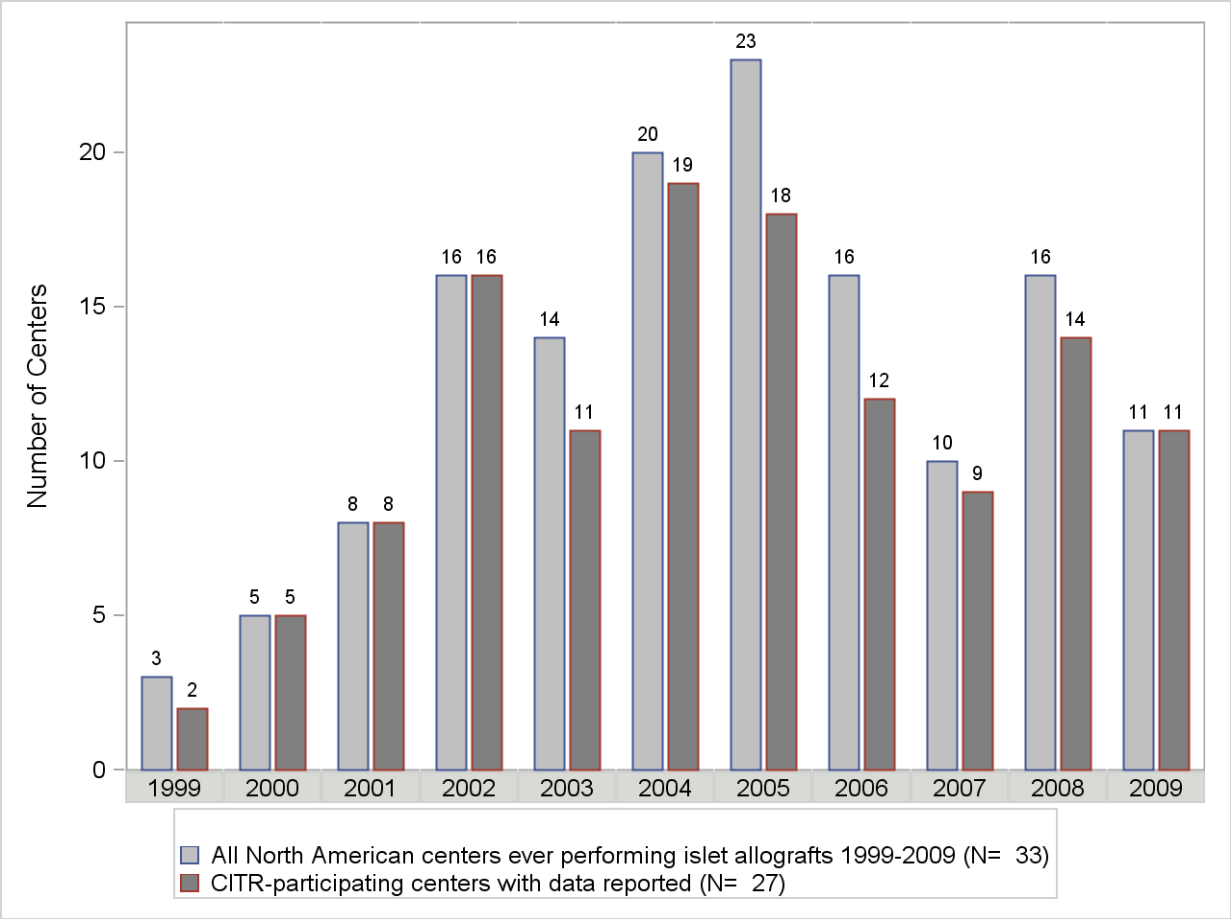
A - CITR Centers with at least one islet allograft infusion procedure conducted and reported to CITR in 2009
B – CITR Centers with data reports pending

Exhibit 1 – 2C
Islet Transplant Centers Reporting Data to CITR
Participating Australian Centers 1999-2009



A - CITR Centers with at least one islet allograft infusion procedure conducted in 2009
C - CITR Centers with no islet allograft infusions in 2009

Exhibit 1 – 3
Number of Islet Transplantation Centers Performing Islet Allografts per Year and Number with Data Entered in CITR Database
North American Islet Transplant Centers 1999-2009

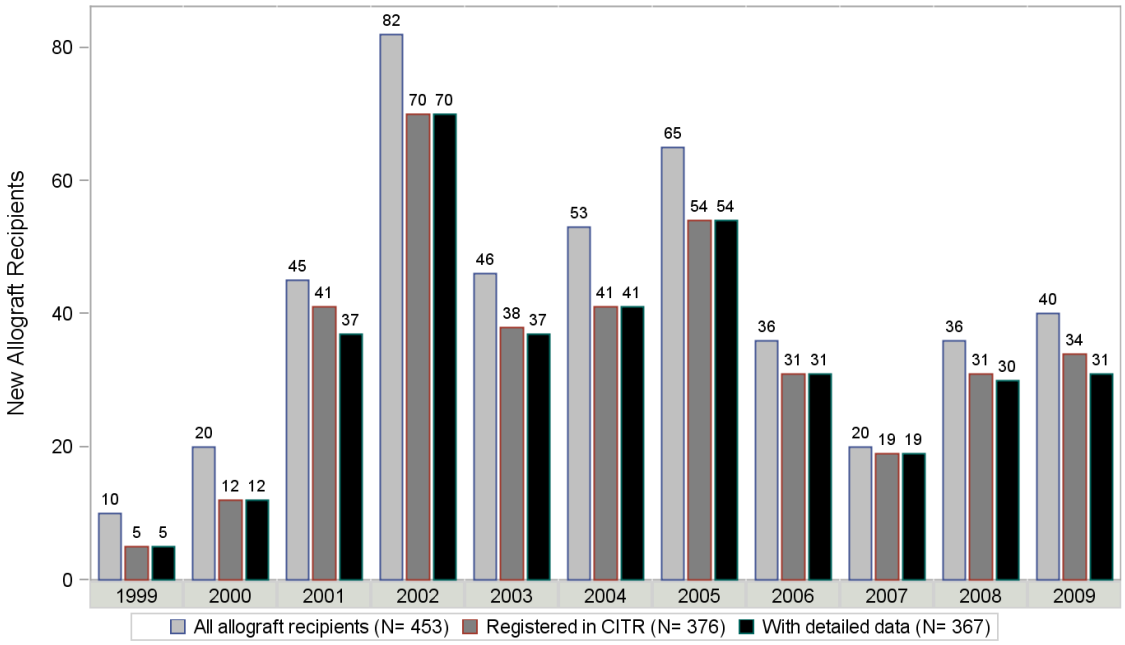


"All North American Centers Performing Islet Allografts" includes sites that reported performing at least one islet infusion procedure in the specified year. "CITR-Participating Centers with Data Entered" represents the number of islet transplant programs in the specified year that have contributed data for the analyses included in this Annual Report.

Since last year's report, there have been no new North American centers conducting allogeneic islet transplantation.

Exhibit 1 – 4
Total Number of Islet Allograft Recipients, Recipients at CITR-Participating Centers, and Recipients with Detailed Data Reported to CITR by Year of First Islet Allograft Infusion

A. Allograft recipients at North American Islet Transplant Centers 1999-2009



From 1999-2009, 453 patients with type 1 diabetes mellitus have received at least one islet allograft infusion procedure in North America. Of these, 376 (83%) consented to and were registered in CITR. Detailed data was available on 367 of these recipients, representing 81% of the overall 453.

B. Allograft recipients at CITR-Participating European and Australian JDRF Centers 1999-2009

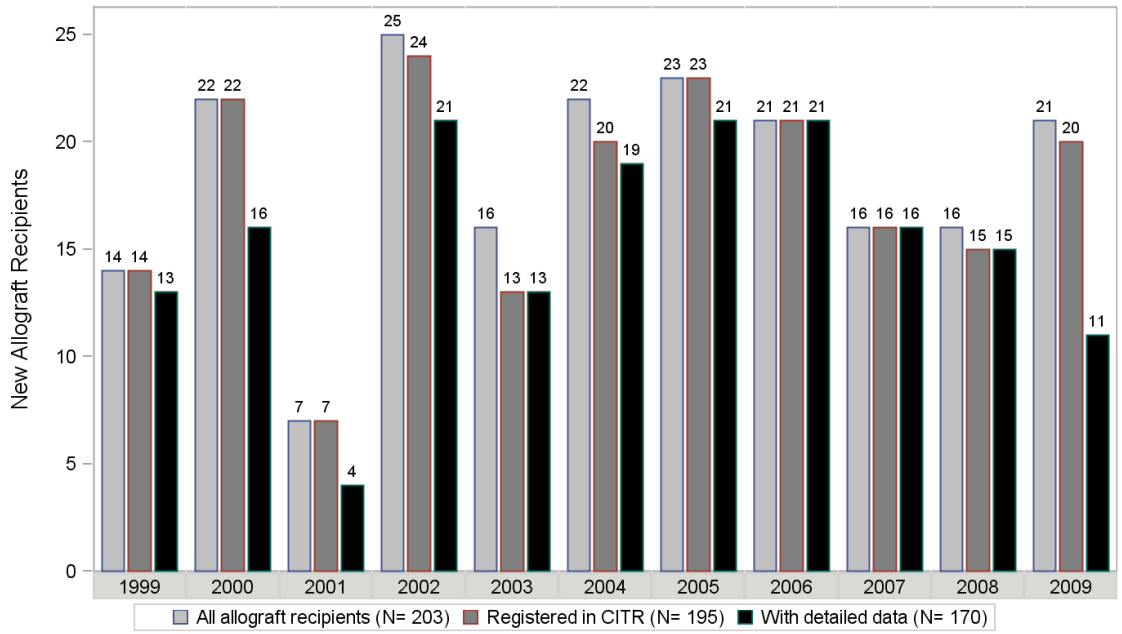
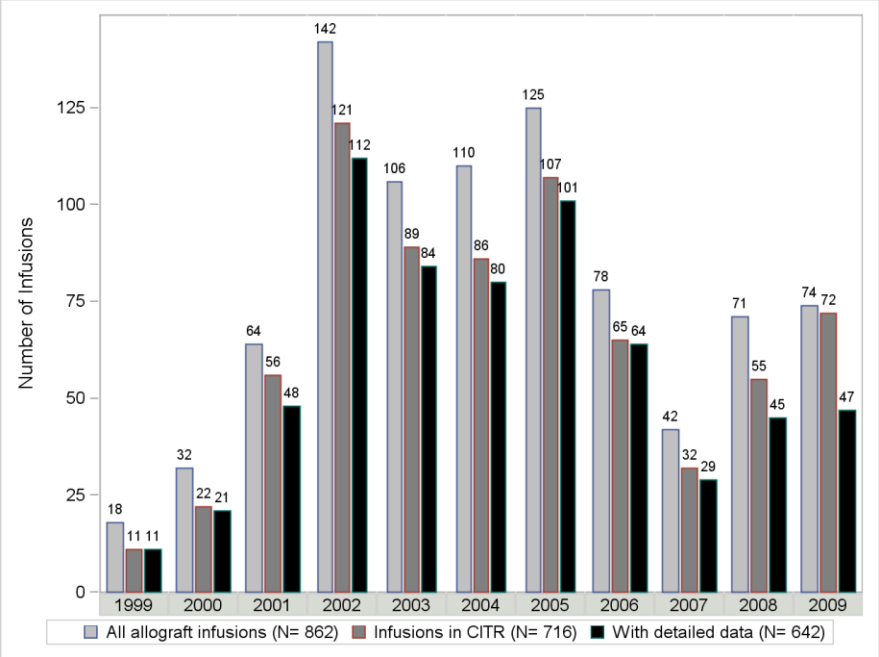


Exhibit 1 – 5
Total Number of Islet Allograft Infusion Procedures Performed and Number with Data Reported to CITR

A. CITR-Participating North American Islet Transplant Centers 1999-2009



From 1999-2009, 453 North American islet transplant recipients of allograft islets received a total of 862 infusion procedures. CITR-participating centers have reported 716 of those 862 (83%) procedures. The Registry has received detailed data relative to 642 allograft infusion procedures, representing 74% of all 862 human-to-human islet allograft infusions performed in North America from 1999-2009.

B. CITR-Participating European and Australian JDRF Centers 1999-2009

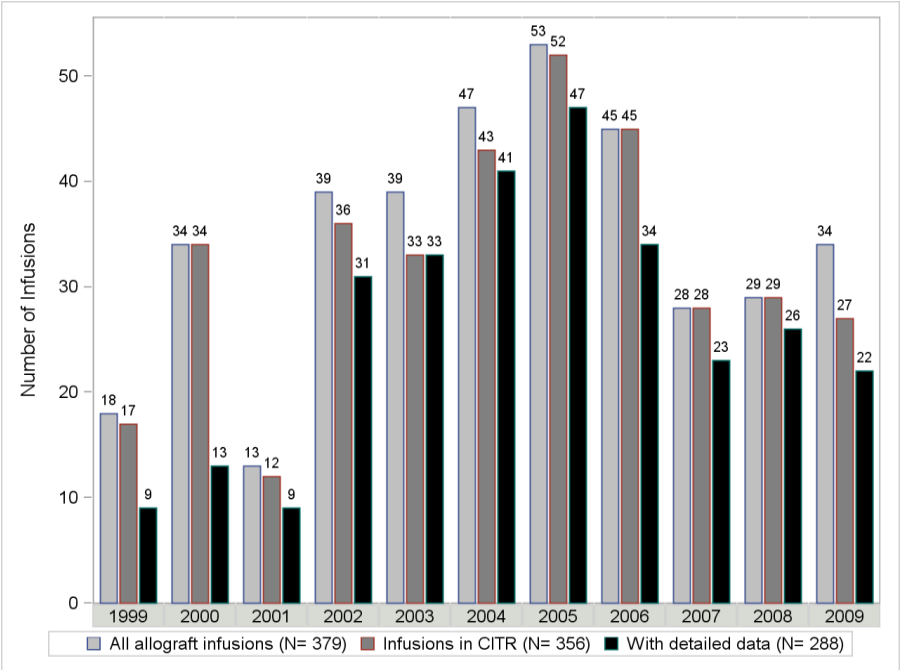
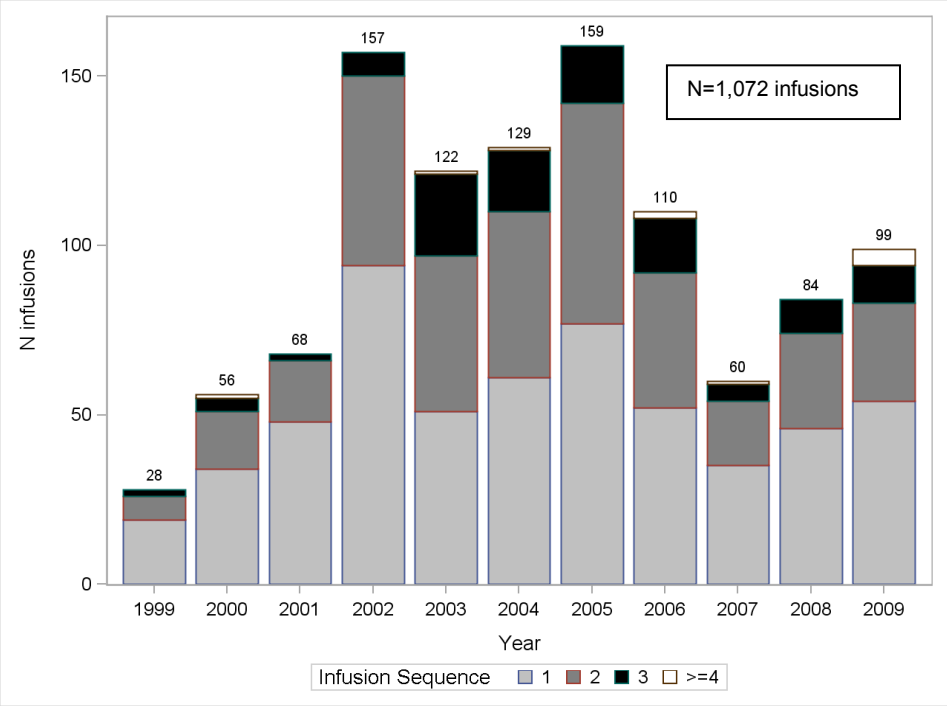


Exhibit 1 – 6

A. Islet Allograft Infusions by Infusion Sequence Number and Year CITR-Participating North American and JDRF Centers, 1999-2009



B. Islet Allograft Recipients by Total Infusions to Date and Year CITR-Participating North American and JDRF Centers, 1999-2009

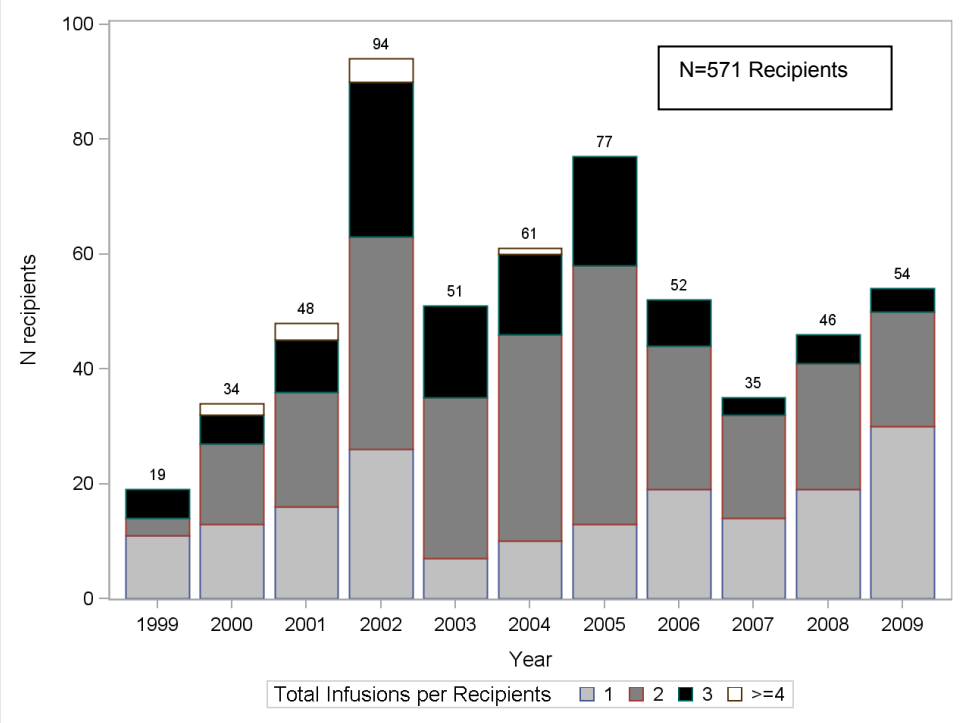


Exhibit 1 – 7
Total Number of Islet Allograft Infusions Per Recipient:
CITR-Participating North American and JDRF Centers, 1999-2009

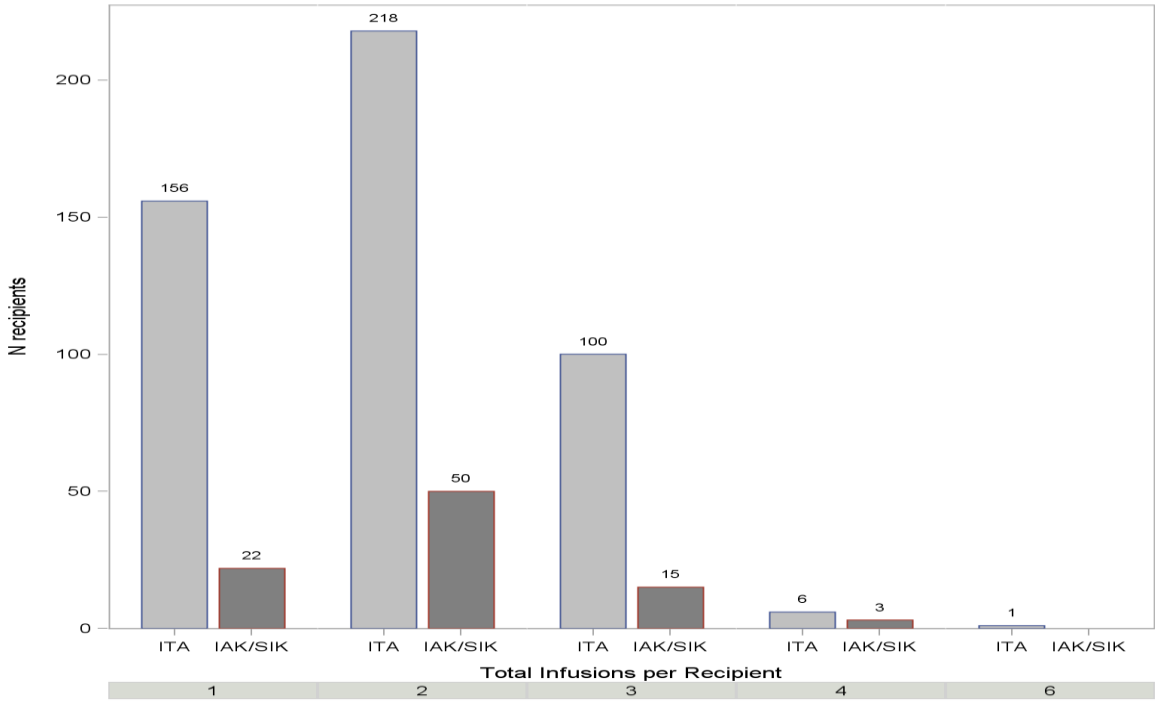


Exhibit 1 – 8
Total Number of Deceased Donors per Islet Allograft Infusion
CITR-Participating North American and JDRF Centers, 1999-2009

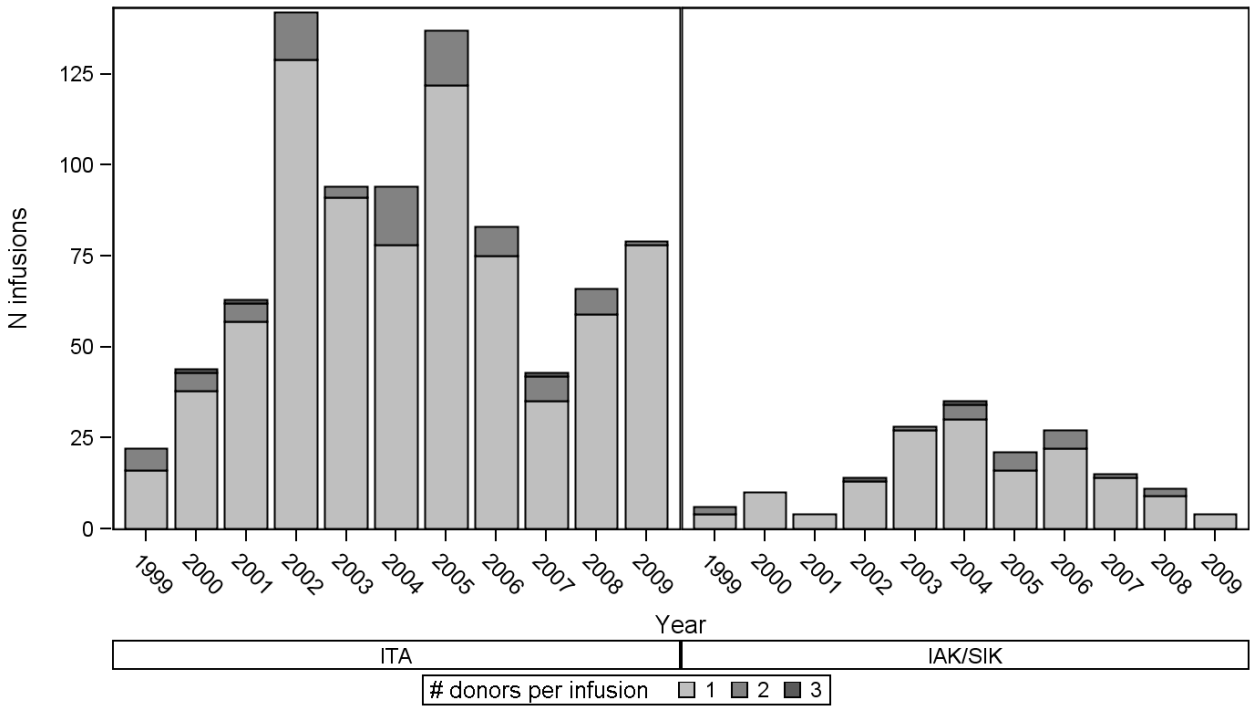


Exhibit 1 – 9

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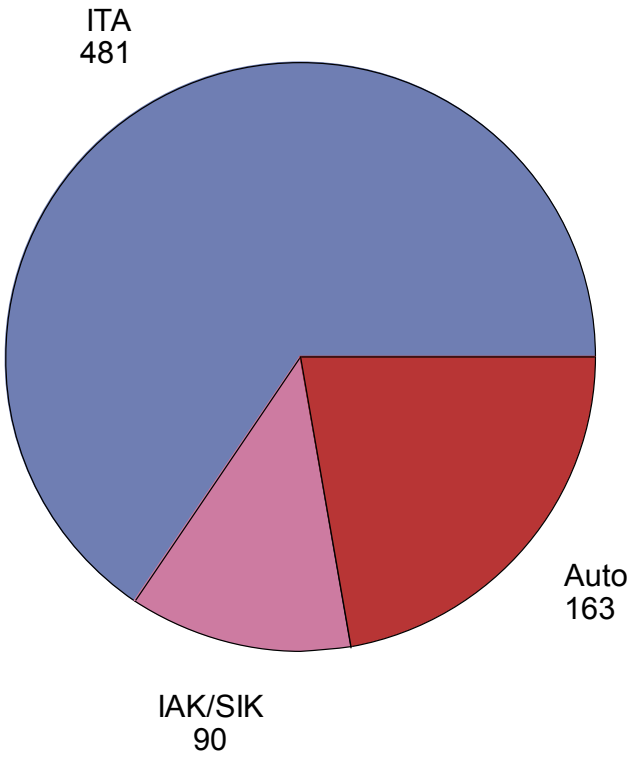

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Chapter 2
Recipient and Donor Characteristics

Introduction

All pre-infusion recipient characteristics are displayed in Exhibits 2-1 to 2-9. The distribution of each characteristic (variable) is shown according to transplant type (ITA or IAK/SIK) and era (1999-2003, 2004-2006, 2007-2009). In the first paired table per variable, the distribution of available data is shown and tested for differences by transplant type and era. Data availability is shown in the second, dimmed, paired table. Nominal p-values are not based on experimental design.

In Exhibits 2-10 to 2-16, multiple donor information has been summarized over any multiple donors/pancreata per islet infusion. There were 960 single-donor, 212 two-donor and 5 three-donor infusions, for a total of 1,187 donors and 1,072 infusions.

Any remarkable results are noted following each exhibit.

Exhibit 2-1
Recipient Demographics

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
		481		**90**			**246**		**190**		**135**		
Gender	**Female**	293	61.4	49	55.1		156	63.7	107	56.9	79	59.4	
	Male	184	38.6	40	44.9		89	36.3	81	43.1	54	40.6	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
Gender	Available	477	99.2	89	98.9		245	99.6	188	98.9	133	98.5	
	Missing	4	0.8	1	1.1		1	0.4	2	1.1	2	1.5	

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Race	**White**	329	98.8	73	98.6		173	98.9	136	98.6	93	98.9	
	Multiple	1	0.3	-	0.0		1	0.6	-	0.0	-	0.0	
	American Indian	1	0.3	-	0.0		-	0.0	1	0.7	-	0.0	
	Black	1	0.3	1	1.4		-	0.0	1	0.7	1	1.1	
	Hawaiian	1	0.3	-	0.0		1	0.6	-	0.0	-	0.0	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Race	Available	333	69.2	74	82.2	407.0	175	71.1	138	72.6	94	69.6	407.0
	Missing	148	30.8	16	17.8	164.0	71	28.9	52	27.4	41	30.4	164.0

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Ethnicity	**Not Hispanic**	325	97.6	71	97.3		172	98.3	130	94.9	94	100.0	
	Hispanic	8	2.4	2	2.7		3	1.7	7	5.1	-	0.0	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
Ethnicity	Available	333	69.2	73	81.1		175	71.1	137	72.1	94	69.6	
	Missing	148	30.8	17	18.9		71	28.9	53	27.9	41	30.4	

* = p <.05; ** = p <.01; *** = p <.001

Race and ethnicity are not collected at the JDRF sites.

Exhibit 2-1 (continued)
Recipient Demographics

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Employment	**Full time**	206	58.7	22	36.7	***	105	58.7	86	54.1	37	50.7	
	Not working disease	53	15.1	24	40.0		32	17.9	32	20.1	13	17.8	
	Not working by choice	22	6.3	2	3.3		8	4.5	10	6.3	6	8.2	
	Part time by choice	23	6.6	3	5.0		9	5.0	9	5.7	8	11.0	
	Retired	18	5.1	-	0.0		4	2.2	11	6.9	3	4.1	
	Part time by disease	19	5.4	3	5.0		16	8.9	4	2.5	2	2.7	
	Not working unknown	4	1.1	4	6.7		2	1.1	3	1.9	3	4.1	
	Part time unknown	2	0.6	-	0.0		1	0.6	1	0.6	-	0.0	
	Student	3	0.9	2	3.3		2	1.1	2	1.3	1	1.4	
	Not working no employ	1	0.3	-	0.0		-	0.0	1	0.6	-	0.0	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
Employment	**Available**	351	73.0	60	66.7		179	72.8	159	83.7	73	54.1	
	Missing	130	27.0	30	33.3		67	27.2	31	16.3	62	45.9	

* = p <.05; ** = p <.01; *** = p <.001

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Exhibit 2-3
Recipient Characteristics at First Infusion

		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Indication for ITx	**Unknown/Missing**	15	3.1	1	1.1		4	1.6	-	-	12	8.9	
	Cystic fibrosis	3	0.6	-	-		1	0.4	-	-	2	1.5	
	Pancreatectomy	1	0.2	-	-		-	-	-	-	1	0.7	
	T1D	462	96.0	89	98.9		241	98.0	190	100.0	120	88.9	

	ITA			IAK/SIK				1999-2003			2004-2006			2007-2009			
	N	Mean	SE	N	Mean	SE	p	N	Mean	SE	N	Mean	SE	N	Mean	SE	p
Age at Transplant	471	44.8	0.5	90	45.3	0.8		246	42.4	0.6	190	45.4	135	48.7	0.8		**
Days listed	370	308.0	18.0	76	289.7	35.5		204	224.2	16.4	171	324.4	25.6	71	489.5	59.5	***
Duration of Diabetes (yrs)	456	27.7	0.6	89	32.6	0.9	***	241	26.3	0.8	190	29.4	0.8	114	31.7	1.2	***
Weight (kg)	427	66.0	0.5	85	61.8	1.0	***	219	65.0	0.7	181	65.5	0.8	112	65.6	0.9	
Body mass index (kg/m2)	414	23.6	0.1	84	22.5	0.3	**	213	23.4	0.2	180	23.3	0.2	105	23.5	0.3	
Daily insulin requirement prior to infusion (units)	370	34.9	0.8	74	35.2	1.5		197	36.3	1.1	172	34.9	1.2	75	31.5	1.5	*
Duration of intensive therapy (yrs)	240	18.8	0.9	14	24.0	4.1		126	18.1	1.1	88	21.3	1.5	40	17.4	2.6	
Avg daily insulin / kg recipient body weight	365	0.5	0.0	72	0.6	0.0		197	0.6	0.0	167	0.5	0.0	73	0.5	0.0	**
Fasting plasma glucose (mg/dL)	371	180.8	5.5	75	183.9	12.1		195	199.9	8.3	160	169.4	7.7	91	162.7	9.3	**
Basal C-Peptide (ng/mL)	326	0.2	0.0	82	0.1	0.0		175	0.3	0.0	147	0.1	0.0	86	0.1	0.0	***
HbA1C (%)	408	7.8	0.1	85	7.9	0.1		210	7.8	0.1	181	7.8	0.1	102	7.8	0.1	
Class I PRA (%)	323	3.3	0.7	49	1.6	1.0		165	2.4	0.7	144	4.1	1.3	63	2.7	1.1	
Class II PRA (%)	196	3.0	0.9	11	0.0	0.0		89	1.6	1.1	71	3.8	1.6	47	4.0	1.9	

* = p <.05; ** = p <.01; *** = p <.001

Mean recipient age has increased over the decade, as has mean waiting time and duration of diabetes.

While some recipients with basal C-peptide > 0.3 ng/ml were transplanted in 1999-2006, no islet allograft recipient had positive C-peptide pre-transplant in the recent era.

Exhibit 2-4
Recipient Diabetes Characteristics and Medical History

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Number of injections per day	**1-2**	2	3.8	8	3.4		7	5.4	1	0.9	2	4.8	
	3-5	48	90.6	220	94.4		120	93.0	112	97.4	36	85.7	*
	6 or more	3	5.7	5	2.1	8.000	2	1.6	2	1.7	4	9.5	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
Number of injections per day	Available	233	48.4	53	58.9		129	52.4	115	60.5	42	31.1	
	Missing	248	51.6	37	41.1		117	47.6	75	39.5	93	68.9	

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Use of insulin pump	**No**	257	64.6	65	77.4	*	147	70.3	126	68.5	49	55.1	*
	Yes	141	35.4	19	22.6		62	29.7	58	31.5	40	44.9	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
Use of insulin pump	Available	398	82.7	84	93.3		209	85.0	184	96.8	89	65.9	
	Missing	83	17.3	6	6.7		37	15.0	6	3.2	46	34.1	

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Hypoglycemia status	**Unaware**	281	70.6	36	44.4	***	129	62.0	128	69.9	60	68.2	**
	Partial aware	107	26.9	20	24.7		65	31.3	45	24.6	17	19.3	
	No Occurrence	2	0.5	4	4.9		4	1.9	1	0.5	1	1.1	
	Aware	8	2.0	21	25.9		10	4.8	9	4.9	10	11.4	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
Hypoglycemia status	Available	398	82.7	81	90.0		208	84.6	183	96.3	88	65.2	
	Missing	83	17.3	9	10.0		38	15.4	7	3.7	47	34.8	

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Lipid-lowering medication	**No**	270	68.0	48	55.2	*	162	76.4	109	59.2	47	53.4	***
	Yes	127	32.0	39	44.8		50	23.6	75	40.8	41	46.6	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
Lipid-lowering medication	Available	397	82.5	87	96.7		212	86.2	184	96.8	88	65.2	
	Missing	84	17.5	3	3.3		34	13.8	6	3.2	47	34.8	

* = p <.05; ** = p <.01; *** = p <.001

Increased use of lipid-lowering medications is noted in the most recent era.

Exhibit 2-4 (continued)
Recipient Diabetes Characteristics and Medical History

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Anti-hypertension medication	**No**	245	61.3	27	31.4	***	126	58.9	103	56.3	43	48.3	
	Yes	155	38.8	59	68.6		88	41.1	80	43.7	46	51.7	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
Anti-hypertension medication	Available	400	83.2	86	95.6		214	87.0	183	96.3	89	65.9	
	Missing	81	16.8	4	4.4		32	13.0	7	3.7	46	34.1	

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Anti-hyperglycemia medication	**No**	44	97.8	14	100.0		7	100.0	21	100.0	30	96.8	
	Yes	1	2.2	-	0.0		-	0.0	-	0.0	1	3.2	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
Anti-hyperglycemia medication	Available	45	9.4	14	15.6		7	2.8	21	11.1	31	23.0	
	Missing	436	90.6	76	84.4		239	97.2	169	88.9	104	77.0	

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Smoker	**No**	339	95.5	58	98.3		168	96.6	156	95.7	73	94.8	
	Yes	16	4.5	1	1.7		6	3.4	7	4.3	4	5.2	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
Smoker	Available	355	73.8	59	65.6		174	70.7	163	85.8	77	57.0	
	Missing	126	26.2	31	34.4		72	29.3	27	14.2	58	43.0	

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Peripheral neuropathy	**No**	257	65.4	37	46.3	**	119	57.8	115	63.2	60	70.6	
	Yes	136	34.6	43	53.8		87	42.2	67	36.8	25	29.4	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
Peripheral neuropathy	Available	393	81.7	80	88.9		206	83.7	182	95.8	85	63.0	
	Missing	88	18.3	10	11.1		40	16.3	8	4.2	50	37.0	

* = p <.05; ** = p <.01; *** = p <.001

Increased use of anti-hypertensives is noted for IAK/SIK.

Exhibit 2-4 (continued)
Recipient Diabetes Characteristics and Medical History

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Autonomic neuropathy	**No**	306	80.5	45	66.2	**	154	76.2	134	80.2	63	79.7	
	Yes	74	19.5	23	33.8		48	23.8	33	19.8	16	20.3	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
Autonomic neuropathy	Available	380	79.0	68	75.6		202	82.1	167	87.9	79	58.5	
	Missing	101	21.0	22	24.4		44	17.9	23	12.1	56	41.5	

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
CAD history	**No**	354	90.1	68	81.0	*	202	94.8	154	85.1	66	79.5	***
	Yes	39	9.9	16	19.0		11	5.2	27	14.9	17	20.5	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
CAD history	Available	393	81.7	84	93.3		213	86.6	181	95.3	83	61.5	
	Missing	88	18.3	6	6.7		33	13.4	9	4.7	52	38.5	

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
CVA history	**No**	382	99.2	73	96.1	*	207	99.0	170	98.8	78	97.5	
	Yes	3	0.8	3	3.9		2	1.0	2	1.2	2	2.5	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
CVA history	Available	385	80.0	76	84.4		209	85.0	172	90.5	80	59.3	
	Missing	96	20.0	14	15.6		37	15.0	18	9.5	55	40.7	

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
PVD history	**No**	364	96.6	54	79.4	***	191	95.0	159	94.1	68	90.7	
	Yes	13	3.4	14	20.6		10	5.0	10	5.9	7	9.3	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
PVD history	Available	377	78.4	68	75.6		201	81.7	169	88.9	75	55.6	
	Missing	104	21.6	22	24.4		45	18.3	21	11.1	60	44.4	

* = p <.05; ** = p <.01; *** = p <.001

Increased prevalence of CAD history is noted for the most recent era.

Exhibit 2-4 (continued)
Recipient Diabetes Characteristics and Medical History

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Retinopathy	**No**	167	43.3	3	3.6	***	67	31.5	69	39.7	34	41.5	
	Yes	219	56.7	80	96.4		146	68.5	105	60.3	48	58.5	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
Retinopathy	Available	386	80.2	83	92.2		213	86.6	174	91.6	82	60.7	
	Missing	95	19.8	7	7.8		33	13.4	16	8.4	53	39.3	

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Macular edema	**No**	346	97.7	50	92.6	*	176	97.2	154	96.9	66	97.1	
	Yes	8	2.3	4	7.4		5	2.8	5	3.1	2	2.9	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
Macular edema	Available	354	73.6	54	60.0		181	73.6	159	83.7	68	50.4	
	Missing	127	26.4	36	40.0		65	26.4	31	16.3	67	49.6	

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Blood group	**A**	233	50.1	43	48.3		126	52.3	95	50.0	55	44.7	
	O	174	37.4	34	38.2		85	35.3	76	40.0	47	38.2	*
	B	54	11.6	10	11.2		29	12.0	19	10.0	16	13.0	
	AB	-	0.0	1	1.1		1	0.4	-	0.0	-	0.0	
	A2	1	0.2	-	0.0		-	0.0	-	0.0	1	0.8	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
Blood group	Available	462	96.0	88	97.8		241	98.0	190	100.0	119	88.1	
	Missing	19	4.0	2	2.2		5	2.0	-	0.0	16	11.9	

* = p <.05; ** = p <.01; *** = p <.001

A significantly higher proportion of IAK/SIK recipients had retinopathy at baseline.

Exhibit 2-5
Recipient Autoantibodies and Sensitization at First Infusion

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Pre transplant autoantibody GAD 65	**Negative**	196	68.8	40	70.2		106	67.5	82	67.2	48	76.2	
	Positive	89	31.2	17	29.8		51	32.5	40	32.8	15	23.8	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
Pre transplant autoantibody GAD 65	Available	285	59.3	57	63.3		157	63.8	122	64.2	63	46.7	
	Missing	196	40.7	33	36.7		89	36.2	68	35.8	72	53.3	

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Pre transplant autoantibody IA-2	**Negative**	366	85.9	81	93.1		190	84.1	163	88.1	94	92.2	
	Positive	60	14.1	6	6.9		36	15.9	22	11.9	8	7.8	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
Pre transplant autoantibody IA-2	Available	426	88.6	87	96.7		226	91.9	185	97.4	102	75.6	
	Missing	55	11.4	3	3.3		20	8.1	5	2.6	33	24.4	

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Pre transplant autoantibody Insulin	**Negative**	285	66.9	67	77.0		157	69.5	117	63.2	78	76.5	
	Positive	141	33.1	20	23.0		69	30.5	68	36.8	24	23.5	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
Pre transplant autoantibody Insulin	Available	426	88.6	87	96.7		226	91.9	185	97.4	102	75.6	
	Missing	55	11.4	3	3.3		20	8.1	5	2.6	33	24.4	

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Total Number of Positive Autoantibodies	**0**	210	49.3	54	62.1	**	107	47.3	94	50.8	63	61.8	*
	1/4	129	30.3	22	25.3		69	30.5	54	29.2	28	27.5	
	1/3	5	1.2	-	0.0		4	1.8	1	0.5	-	0.0	
	1/2	67	15.7	11	12.6		40	17.7	29	15.7	9	8.8	
	3/4	15	3.5	-	0.0		6	2.7	7	3.8	2	2.0	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
Total Number of Positive Autoantibodies	Available	426	88.6	87	96.7		226	91.9	185	97.4	102	75.6	
	Missing	55	11.4	3	3.3		20	8.1	5	2.6	33	24.4	

* = p <.05; ** = p <.01; *** = p <.001

Exhibit 2-5 (continued)
Recipient Autoantibodies and Sensitization at First Infusion

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
PRA-Class I	Neg	270	83.1	45	91.8		139	84.2	124	85.5	52	81.3	
	Pos	55	16.9	4	8.2		26	15.8	21	14.5	12	18.8	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
PRA-Class I	Available	325	67.6	49	54.4		165	67.1	145	76.3	64	47.4	
	Missing	156	32.4	41	45.6		81	32.9	45	23.7	71	52.6	

Available data		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
PRA-Class II	Neg	176	88.9	11	100.0		85	95.5	61	85.9	41	83.7	
	Pos	20	10.1	-	0.0		4	4.5	10	14.1	6	12.2	*
	Equ	2	1.0	-	0.0		-	0.0	-	0.0	2	4.1	

Data completeness		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%		N	%	N	%	N	%	
PRA-Class II	Available	198	41.2	11	12.2		89	36.2	71	37.4	49	36.3	
	Missing	283	58.8	79	87.8		157	63.8	119	62.6	86	63.7	

* = p <.05; ** = p <.01; *** = p <.001

Exhibit 2-6
Recipient Infectious Disease Testing at First Infusion

		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
HIV	**UNK**	90	18.7	23	25.6		42	17.1	26	13.7	45	33.3	
	NEG	391	81.3	66	73.3		204	82.9	164	86.3	89	65.9	
	POS	-	0.0	1	1.1		-	0.0	-	0.0	1	0.7	
CMV-IgG	**UNK**	84	17.5	13	14.4		40	16.3	24	12.6	33	24.4	
	NEG	214	44.5	33	36.7		104	42.3	88	46.3	55	40.7	
	POS	183	38.0	44	48.9		102	41.5	78	41.1	47	34.8	
CMV-IgM	**UNK**	243	50.5	44	48.9		125	50.8	82	43.2	80	59.3	
	NEG	234	48.6	40	44.4		113	45.9	106	55.8	55	40.7	
	POS	4	0.8	6	6.7	***	8	3.3	2	1.1	-	0.0	*
Hepatitis B Core	**UNK**	150	31.2	36	40.0		97	39.4	42	22.1	47	34.8	
	NEG	326	67.8	51	56.7		147	59.8	146	76.8	84	62.2	
	POS	5	1.0	3	3.3		2	0.8	2	1.1	4	3.0	
Hepatitis B Surface	**UNK**	435	90.4	85	94.4		242	98.4	178	93.7	100	74.1	
	NEG	29	6.0	2	2.2		2	0.8	8	4.2	21	15.6	
	POS	17	3.5	3	3.3		2	0.8	4	2.1	14	10.4	
HCV	**UNK**	92	19.1	11	12.2		49	19.9	17	8.9	37	27.4	
	NEG	387	80.5	77	85.6		194	78.9	173	91.1	97	71.9	
	POS	2	0.4	2	2.2		3	1.2	-	0.0	1	0.7	
EBV-IgG	**UNK**	98	20.4	14	15.6		51	20.7	21	11.1	40	29.6	
	NEG	36	7.5	2	2.2		15	6.1	12	6.3	11	8.1	
	POS	347	72.1	74	82.2		180	73.2	157	82.6	84	62.2	
EBV-IgM	**UNK**	262	54.5	36	40.0		128	52.0	86	45.3	84	62.2	
	NEG	186	38.7	47	52.2		95	38.6	90	47.4	48	35.6	
	POS	33	6.9	7	7.8		23	9.3	14	7.4	3	2.2	

* = p <.05; ** = p <.01; *** = p <.001

Exhibit 2-7
Recipient Characteristics Prior to First Infusion by Total Number of Infusions Received

	ITA									IAK/SIK								
	Total Number of Infusions Received									Total Number of Infusions Received								
	One Infusion			Two Infusions			>= Three Infusions			One Infusion			Two Infusions			>= Three Infusions		
	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE
Age (yrs)	156	45.3	0.8	218	46.2	0.7	107	41.5	0.9	22	43.5	2.3	50	46.1	1.0	18	45.2	1.5
Duration of Diabetes (yrs)	138	26.7	1.2	212	28.8	0.8	106	26.8	1.0	22	31.4	2.5	49	33.3	1.1	18	32.1	1.1
Weight (kg)	123	63.2	0.9	204	66.9	0.8	100	67.8	1.0	20	59.2	2.4	48	61.4	1.3	17	65.9	1.8
Body Mass Index (kg/m2)	117	23.1	0.3	199	23.8	0.2	98	23.8	0.3	19	21.3	0.6	48	22.7	0.4	17	23.4	0.6
Daily insulin requirement (units)	87	32.2	1.4	183	34.5	1.1	100	38.2	1.7	18	34.2	2.6	41	35.0	2.0	15	37.0	4.1
Average daily insulin / kg recipient body weight	87	0.5	0.0	181	0.5	0.0	97	0.6	0.0	16	0.6	0.1	41	0.6	0.0	15	0.5	0.0
Duration of intensive insulin therapy (yrs)	58	16.1	2.0	124	20.9	1.2	58	17.1	1.5	7	29.7	5.2	6	21.2	6.2	1	0.9	-
Fasting plasma glucose (mg/dL)	107	162.5	9.1	164	186.8	8.6	100	190.6	10.7	18	181.4	23.9	43	175.9	13.5	14	211.9	39.8
Basal C-Peptide (ng/mL)	105	0.2	0.0	139	0.2	0.0	82	0.1	0.0	19	0.2	0.1	46	0.1	0.0	17	0.1	0.0
HbA1C (%)	118	7.7	0.1	194	7.8	0.1	96	7.9	0.1	21	7.9	0.3	48	8.0	0.2	16	7.7	0.3

Exhibit 2-8
Recipient Baseline Autoantibodies by Total Infusions Received

		ITA						IAK/SIK					
		Total Number of Infusions Received						Total Number of Infusions Received					
		One Infusion		Two Infusions		>= Three Infusions		One Infusion		Two Infusions		>= Three Infusions	
		N	%	N	%	N	%	N	%	N	%	N	%
Pre transplant autoantibody - GAD 65	**Unknown/Missing**	79	50.6	77	35.3	40	37.4	7	31.8	19	38.0	7	38.9
	Negative	50	32.1	102	46.8	44	41.1	12	54.5	21	42.0	7	38.9
	Positive	27	17.3	39	17.9	23	21.5	3	13.6	10	20.0	4	22.2
Pre transplant autoantibody - IA-2	**Unknown/Missing**	36	23.1	17	7.8	2	1.9	-	-	2	4.0	1	5.6
	Negative	105	67.3	176	80.7	85	79.4	17	77.3	47	94.0	17	94.4
	Positive	15	9.6	25	11.5	20	18.7	5	22.7	1	2.0	-	-
Pre transplant autoantibody - Insulin	**Unknown/Missing**	36	23.1	17	7.8	2	1.9	-	-	2	4.0	1	5.6
	Negative	92	59.0	129	59.2	64	59.8	15	68.2	37	74.0	15	83.3
	Positive	28	17.9	72	33.0	41	38.3	7	31.8	11	22.0	2	11.1
Total Number of Positive Autoantibodies	**Unknown/Missing**	36	23.1	17	7.8	2	1.9	-	-	2	4.0	1	5.6
	0	63	40.4	98	45.0	49	45.8	11	50.0	31	62.0	12	66.7
	1/4	34	21.8	65	29.8	30	28.0	6	27.3	12	24.0	4	22.2
	1/3	-	-	2	0.9	3	2.8	-	-	-	-	-	-
	1/2	16	10.3	34	15.6	17	15.9	5	22.7	5	10.0	1	5.6
	3/4	7	4.5	2	0.9	6	5.6	-	-	-	-	-	-

Exhibit 2-9
Recipient Laboratory Values at First Infusion

	ITA			IAK/SIK				1999-2003			2004-2006			2007-2009			
	N	Mean	SE	N	Mean	SE	p	N	Mean	SE	N	Mean	SE	N	Mean	SE	p
HbA1C (%)	408	7.8	0.1	85	7.9	0.1		210	7.8	0.1	181	7.8	0.1	102	7.8	0.1	
Basal C-Peptide (ng/mL)	330	0.2	0.0	83	0.1	0.0		177	0.3	0.0	148	0.1	0.0	88	0.1	0.0	***
Fasting blood glucose (mg/dL)	371	180.8	5.5	75	183.9	12.1		195	199.9	8.3	160	169.4	7.7	91	162.7	9.3	**
ALT (U/L)	389	23.2	0.7	73	26.1	1.7		199	22.2	0.9	167	24.2	0.8	96	25.5	1.8	*
AST (U/L)	397	25.8	0.9	74	28.9	1.8		207	24.2	0.7	173	25.7	0.7	91	32.3	3.5	***
Alkaline phosphatase (U/L)	397	84.7	2.5	73	137.3	11.2	***	200	92.6	4.4	169	100.0	5.2	101	81.3	4.8	
Total bilirubin (mg/dL)	397	0.6	0.0	73	0.6	0.0		202	0.6	0.0	170	0.6	0.0	98	0.7	0.0	
Total cholesterol (mg/dL)	394	173.3	1.7	78	181.6	4.3		206	176.8	2.4	178	172.9	2.3	88	173.3	4.5	
HDL (mg/dL)	379	64.0	0.9	70	67.9	2.3		199	64.6	1.2	175	64.0	1.4	75	66.2	2.1	
LDL (mg/dL)	361	93.8	1.4	62	94.8	3.5		180	95.5	1.9	167	94.1	2.0	76	89.8	3.7	
Triglycerides (mg/dL)	394	50.0	1.7	77	67.1	5.0	***	206	53.2	2.5	177	54.8	3.0	88	47.8	2.9	
eGFR-CKD (mL/min/1.73m2)	430	83.0	1.1	86	54.4	2.4	***	218	78.3	1.9	186	77.7	1.8	112	78.8	2.2	

* = p<.05; ** = p<.01; *** = p<.001

Recipients' fasting blood glucose declined over the decade.

Exhibit 2-10
Donor Demographics

		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Gender	Female	307	37.6	69	42.9		151	38.3	137	36.9	88	41.5	
	Male	479	58.7	82	50.9		227	57.6	212	57.1	122	57.5	
	Mixed	30	3.7	10	6.2		16	4.1	22	5.9	2	0.9	

Data completeness		ITA		IAK/SIK		1999-2003		2004-2006		2007-2009	
		N	%	N	%	N	%	N	%	N	%
Gender	Available	816	91.0	161	92.0	394	91.4	371	92.1	212	89.1
	Missing	81	9.0	14	8.0	37	8.6	32	7.9	26	10.9

		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Race	White	770	88.8	164	93.7		401	93.9	345	86.9	188	86.2	
	Non-white	97	11.2	11	6.3		26	6.1	52	13.1	30	13.8	

Data completeness		ITA		IAK/SIK		1999-2003		2004-2006		2007-2009	
		N	%	N	%	N	%	N	%	N	%
Race	Available	867	96.7	175	100.0	427	99.1	397	98.5	218	91.6
	Missing	30	3.3	0	0.0	4	0.9	6	1.5	20	8.4

		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Ethnicity	Non Hispanic	441	90.9	75	90.4		235	92.2	198	88.8	83	92.2	
	Hispanic	36	7.4	5	6.0		14	5.5	20	9.0	7	7.8	
	Mixed	8	1.6	3	3.6		6	2.4	5	2.2	0	0.0	

Data completeness		ITA		IAK/SIK		1999-2003		2004-2006		2007-2009	
		N	%	N	%	N	%	N	%	N	%
Ethnicity	Available	485	54.1	83	47.4	255	59.2	223	55.3	90	37.8
	Missing	412	45.9	92	52.6	176	40.8	180	44.7	148	62.2

Exhibit 2-11
Donor Characteristics

	ITA			IAK/SIK			p	1999-2003			2004-2006			2007-2009			p
	N	Mean	SE	N	Mean	SE		N	Mean	SE	N	Mean	SE	N	Mean	SE	
Age (yrs)	677	43.3	0.5	125	44.7	1.2		380	42.7	0.6	287	44.0	0.7	135	44.9	1.1	
Weight (kg)	808	87.3	0.7	158	84.5	1.8		389	84.9	1.0	375	86.5	1.0	202	91.3	1.5	***
Height (m)	813	173.3	0.4	164	172.8	0.7		391	173.1	0.5	378	173.1	0.5	208	173.5	0.8	
Body Mass Index(kg/m2)	806	29.1	0.2	158	28.3	0.6		387	28.3	0.3	375	28.8	0.3	202	30.3	0.4	***

		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Donor blood type	**A**	377	46.0	71	43.6		193	48.9	165	43.9	90	42.7	
	O	428	52.3	88	54.0		195	49.4	202	53.7	119	56.4	
	B	11	1.3	3	1.8		6	1.5	6	1.6	2	0.9	
	AB	3	0.4	1	0.6		1	0.3	3	0.8	0	0.0	

Data completeness		ITA		IAK/SIK		1999-2003		2004-2006		2007-2009	
		N	%	N	%	N	%	N	%	N	%
Donor blood type	Available	819	91.3	163	93.1	395	91.6	376	93.3	211	88.7
	Missing	78	8.7	12	6.9	36	8.4	27	6.7	27	11.3

		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Hx Hypertension	**No**	439	63.0	79	64.8		185	62.7	219	65.0	114	61.0	
	Yes	258	37.0	43	35.2		110	37.3	118	35.0	73	39.0	

Data completeness		ITA		IAK/SIK		1999-2003		2004-2006		2007-2009	
		N	%	N	%	N	%	N	%	N	%
Hx Hypertension	Available	697	77.7	122	69.7	295	68.4	337	83.6	187	78.6
	Missing	200	22.3	53	30.3	136	31.6	66	16.4	51	21.4

* = p<.05; ** = p<.01; *** = p<.001

Over the decade, donor weight and BMI have increased notably.

Exhibit 2-11 (continued)
Donor Characteristics

		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Hx Alcohol	No	526	80.8	93	77.5		233	81.8	250	77.4	136	83.4	
	Yes	125	19.2	27	22.5		52	18.2	73	22.6	27	16.6	

Data completeness		ITA		IAK/SIK		1999-2003		2004-2006		2007-2009	
		N	%	N	%	N	%	N	%	N	%
Hx Alcohol	Available	651	72.6	120	68.6	285	66.1	323	80.1	163	68.5
	Missing	246	27.4	55	31.4	146	33.9	80	19.9	75	31.5

		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Hx Diabetes	No	740	99.9	130	100.0		351	100.0	348	100.0	171	99.4	
	Yes	1	0.1	0	0.0		0	0.0	0	0.0	1	0.6	

Data completeness		ITA		IAK/SIK		1999-2003		2004-2006		2007-2009	
		N	%	N	%	N	%	N	%	N	%
Hx Diabetes	Available	741	82.6	130	74.3	351	81.4	348	86.4	172	72.3
	Missing	156	17.4	45	25.7	80	18.6	55	13.6	66	27.7

Exhibit 2-12
Donor Hospitalization

		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Cause of death	Not reported	98	10.9	19	10.9		50	11.6	34	8.4	33	13.9	
	Anoxia/cardiac arrest	34	3.8	7	4.0		15	3.5	11	2.7	15	6.3	
	Head trauma	238	26.5	35	20.0		106	24.6	101	25.1	66	27.7	
	Cerebrovascular/stroke	412	45.9	89	50.9		193	44.8	200	49.6	108	45.4	No Testing
	CNS tumor	4	0.4	1	0.6		4	0.9	1	0.2	-	0.0	
	Mixed	44	4.9	11	6.3		18	4.2	29	7.2	8	3.4	
	Not available	14	1.6	9	5.1		15	3.5	8	2.0	-	0.0	
	Other	53	5.9	4	2.3		30	7.0	19	4.7	8	3.4	

	ITA			IAK/SIK				1999-2003			2004-2006			2007-2009			
	N	Mean	SE	N	Mean	SE	p	N	Mean	SE	N	Mean	SE	N	Mean	SE	p
Time from admission to brain death (hrs)	480	50.4	3.0	98	51.2	5.2		251	47.5	3.6	234	53.0	4.5	93	52.7	6.0	
Time from cross clamp to pancreas recovery (mins)	482	0.7	0.1	125	0.9	0.0		212	0.6	0.0	269	0.9	0.1	126	0.7	0.1	
Cold ischemia time (hrs)	677	7.3	0.1	124	5.7	0.4	***	342	6.9	0.2	322	7.4	0.2	137	6.7	0.4	

* = p <.05; ** = p <.01; *** = p <.001

Exhibit 2-12 (continued)
Donor Hospitalization

		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Vasopressors used	**Yes**	839	96.8	164	93.7		418	97.9	378	95.2	207	95.0	
	No	28	3.2	11	6.3		9	2.1	19	4.8	11	5.0	

Data completeness		ITA		IAK/SIK		1999-2003		2004-2006		2007-2009	
		N	%	N	%	N	%	N	%	N	%
Vasopressors used	Available	867	96.7	175	100.0	427	99.1	397	98.5	218	91.6
	Missing	30	3.3	0	0.0	4	0.9	6	1.5	20	8.4

		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Transfusions during hospitalization	**No**	588	67.8	115	65.7		273	63.9	271	68.3	159	72.9	
	Yes	279	32.2	60	34.3		154	36.1	126	31.7	59	27.1	

Data completeness		ITA		IAK/SIK		1999-2003		2004-2006		2007-2009	
		N	%	N	%	N	%	N	%	N	%
Transfusions during hospitalization	Available	867	96.7	175	100.0	427	99.1	397	98.5	218	91.6
	Missing	30	3.3	00	0.0	4	0.9	6	1.5	20	8.4

		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Transfusions intraoperatively	**No**	814	93.9	162	92.6		396	92.7	374	94.2	206	94.5	
	Yes	53	6.1	13	7.4		31	7.3	23	5.8	12	5.5	

Data completeness		ITA		IAK/SIK		1999-2003		2004-2006		2007-2009	
		N	%	N	%	N	%	N	%	N	%
Transfusions intraoperatively	Available	867	96.7	175	100.0	427	99.1	397	98.5	218	91.6
	Missing	30	3.3	0	0.0	4	0.9	6	1.5	20	8.4

Exhibit 2-12 (continued)
Donor Hospitalization

		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Steroids given to donor during hospitalization	**Yes**	266	60.2	46	49.5		126	65.3	123	48.8	63	70.0	***
	No	176	39.8	47	50.5		67	34.7	129	51.2	27	30.0	

Data completeness		ITA		IAK/SIK		1999-2003		2004-2006		2007-2009	
		N	%	N	%	N	%	N	%	N	%
Steroids given to donor during hospitalization	Available	442	49.3	93	53.1	193	44.8	252	62.5	90	37.8
	Missing	455	50.7	82	46.9	238	55.2	151	37.5	148	62.2

		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Insulin given to donor during hospitalization	**No**	362	55.1	72	66.7	*	192	67.8	174	55.8	68	40.0	***
	Yes	295	44.9	36	33.3		91	32.2	138	44.2	102	60.0	

Data completeness		ITA		IAK/SIK		1999-2003		2004-2006		2007-2009	
		N	%	N	%	N	%	N	%	N	%
Insulin given to donor during hospitalization	Available	657	73.2	108	61.7	283	65.7	312	77.4	170	71.4
	Missing	240	26.8	67	38.3	148	34.3	91	22.6	68	28.6

* = p <.05; ** = p <.01; *** = p <.001

Insulin has increasingly been given to donors over the decade.

Exhibit 2-13
Donor Serology

		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
HIV	UNK	146	16.3	33	18.9		61	14.2	50	12.4	68	28.6	
	NEG	751	83.7	142	81.1		370	85.8	353	87.6	170	71.4	
HTLV	UNK	246	27.4	58	33.1		119	27.6	94	23.3	91	38.2	
	NEG	651	72.6	117	66.9		312	72.4	309	76.7	147	61.8	
VDRL	UNK	225	25.1	52	29.7		106	24.6	82	20.3	89	37.4	
	NEG	671	74.8	123	70.3		325	75.4	320	79.4	149	62.6	
	POS	1	0.1	-	0.0		-	0.0	1	0.2	-	0.0	
CMV	UNK	189	21.1	37	21.1		78	18.1	72	17.9	76	31.9	
	NEG	302	33.7	56	32.0		146	33.9	145	36.0	67	28.2	
	POS	406	45.3	82	46.9		207	48.0	186	46.2	95	39.9	
HBSag	UNK	155	17.3	34	19.4		67	15.5	51	12.7	71	29.8	
	NEG	742	82.7	141	80.6		364	84.5	352	87.3	167	70.2	
HBC	UNK	173	19.3	42	24.0		92	21.3	52	12.9	71	29.8	
	NEG	716	79.8	131	74.9		335	77.7	349	86.6	163	68.5	
	POS	8	0.9	2	1.1		4	0.9	2	0.5	4	1.7	
HCV	UNK	156	17.4	39	22.3		74	17.2	51	12.7	70	29.4	
	NEG	741	82.6	135	77.1		357	82.8	352	87.3	167	70.2	
	POS	-	0.0	1	0.6		-	0.0	-	0.0	1	0.4	

No Testing

Exhibit 2-14
Donor Laboratory Data

	ITA			IAK/SIK				1999-2003			2004-2006			2007-2009			
	N	Mean	SE	N	Mean	SE	p	N	Mean	SE	N	Mean	SE	N	Mean	SE	p
Serum creatinine (mg/dL)	639	1.1	0.0	140	1.0	0.0	*	281	1.1	0.0	324	1.1	0.0	174	1.1	0.0	
BUN (mg/dL)	433	15.5	0.4	135	15.3	0.8		232	14.6	0.5	245	15.3	0.5	91	18.1	1.3	**
Total bilirubin (mg/dL)	514	0.9	0.0	130	0.8	0.1		234	0.8	0.0	264	0.9	0.1	146	0.9	0.1	
AST (IU/L)	533	74.4	8.6	135	84.4	18.2		236	91.6	17.8	275	63.0	8.1	157	77.0	13.0	
ALT (IU/L)	559	61.9	7.0	135	68.4	14.0		238	70.9	14.7	276	52.9	6.8	180	68.6	10.0	
Serum lipase (IU/L)	531	69.3	5.1	101	64.8	8.7		251	61.1	6.2	260	77.4	7.2	121	65.2	12.4	
Serum amylase (IU/L)	595	160.2	15.4	133	119.9	18.0		280	164.1	23.5	313	131.4	13.4	135	179.2	39.9	
Minimum pre-insulin blood glucose (mg/dL)	597	126.7	1.6	120	125.5	3.5		312	126.9	2.0	310	124.5	2.3	95	131.4	4.3	
Maximum blood glucose (mg/dL)	615	228.5	3.4	121	241.3	8.0		269	245.0	5.9	319	226.3	4.5	148	213.8	5.4	***

* = p <.05; ** = p <.01; *** = p <.001

Donors' stimulated blood glucose had declined significantly over the decade.

Exhibit 2-15
Organ Crossmatch Results

		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
Positive cross match	**No**	472	96.3	116	97.5		214	98.6	232	95.9	142	94.7	
	Yes	18	3.7	3	2.5		3	1.4	10	4.1	8	5.3	

Data completeness		ITA		IAK/SIK		1999-2003		2004-2006		2007-2009	
		N	%	N	%	N	%	N	%	N	%
Positive cross match	**Available**	490	54.6	119	68.0	217	50.3	242	60.0	150	63.0
	Missing	407	45.4	56	32.0	214	49.7	161	40.0	88	37.0

Chapter 3
Pancreas Procurement, Islet Processing, and Infusion Characteristics

Introduction

Chapter 3 describes the pancreas procurement, islet processing, transplant procedure and final islet product information, on the islet products used for clinical transplantation in the recipients in this report, namely those described in Chapter 1.

For the roughly 10% of infusions which derived from more than one donor pancreas, the donor information was collapsed appropriately, either by logical combination (e.g., an infusion product derived from a female donor and a male donor is termed “Mixed”); averaging, (e.g., viability, stimulation index, etc); or summation (e.g., total beta cells, islet particle count, total IEQs infused, etc.) Exhibits 3-1 to 3-4 describe all the variables according to ITA vs. IKA/SIK and by era (1999-2033, 2004-2006, and 2007-2009).

Exhibits 3-5 to 3-7 relate the final islet product characteristics to donor, procurement and processing factors in a univariate manner. Factors that are categorical in nature, e.g., gender, are summarized in Exhibit 3-6, while those that are continuous are shown as correlations with the islet product characteristics in Exhibit 3-7. These results are described more thoroughly in a focus analysis currently in development utilizing multivariate methods.

Exhibit 3-1A
Islet Processing Summary

Final islet preparations for infusion		Transplant type					Era						
		ITA		IAK/SIK			1999-2003		2004-2006		2007-2009		
		N	%	N	%	p	N	%	N	%	N	%	p
		897		**175**			**431**		**398**		**243**		
Procurement team	**Miss/Unk**	170	19.0	22	12.6		57	13.2	50	12.6	85	35.0	
	Unrelated	253	28.2	45	25.7		127	29.5	118	29.6	53	21.8	
	Related	474	52.8	108	61.7		247	57.3	230	57.8	105	43.2	
Islet processing center	**Miss/Unk**												
	Unrelated												
	Related												
Pancreas Preservation	**Missing/Unknown**	61	6.8	6	3.4		27	6.3	6	1.5	34	14.0	
	UW only	359	40.0	83	47.4	**	243	56.4	154	38.7	45	18.5	***
	2L only	188	21.0	22	12.6	*	75	17.4	114	28.6	21	8.6	***
	HTK only	87	9.7	1	0.6	?	-	0.0	33	8.3	55	22.6	*
	Celsior	14	1.6	6	3.4	?	6	1.4	7	1.8	7	2.9	
	UW+2L	33	3.7	8	4.6		15	3.5	20	5.0	6	2.5	
	Other	155	17.3	49	28.0		65	15.1	64	16.1	75	30.9	
Collagenase P	**Miss/Unk**	39	4.3	-	0.0		5	1.2	2	0.5	32	13.2	
	N	837	93.3	174	99.4		423	98.1	379	95.2	209	86.0	
	Y	21	2.3	1	0.6		3	0.7	17	4.3	2	0.8	
Collagenase Serva/NB1	**Miss/Unk**	39	4.3	-	0.0		5	1.2	2	0.5	32	13.2	
	N	739	82.4	161	92.0		424	98.4	379	95.2	97	39.9	
	Y	119	13.3	14	8.0		2	0.5	17	4.3	114	46.9	***
Collagenase Liberase HI	**Miss/Unk**	39	4.3	-	0.0		5	1.2	2	0.5	32	13.2	
	N	317	35.3	67	38.3		54	12.5	134	33.7	196	80.7	
	Y	541	60.3	108	61.7		372	86.3	262	65.8	15	6.2	***
Collagenase Sigmablend	**Miss/Unk**	39	4.3	-	0.0		5	1.2	2	0.5	32	13.2	
	N	856	95.4	175	100.0		426	98.8	396	99.5	209	86.0	
	Y	2	0.2	-	0.0		-	0.0	-	0.0	2	0.8	

* = p <.05; ** = p <.01; *** = p <.001

Exhibit 3-1A
Islet Processing Summary (continued)

Final islet preparations for infusion		Transplant type					Era						
		ITA		IAK/SIK		p	1999-2003		2004-2006		2007-2009		p
		N	%	N	%		N	%	N	%	N	%	
Collagenase Other	**Miss/Unk**	39	4.3	-	0.0		5	1.2	2	0.5	32	13.2	
	N	772	86.1	159	90.9		420	97.4	321	80.7	190	78.2	
	Y	86	9.6	16	9.1		6	1.4	75	18.8	21	8.6	*
Thermolysin	**Miss/Unk**	39	4.3	-	0.0		5	1.2	2	0.5	32	13.2	
	N	805	89.7	167	95.4		425	98.6	340	85.4	207	85.2	
	Y	53	5.9	8	4.6		1	0.2	56	14.1	4	1.6	**
Pulmozyme	**Miss/Unk**	38	4.2	-	0.0		5	1.2	2	0.5	31	12.8	
	N	495	55.2	113	64.6		345	80.0	160	40.2	103	42.4	
	Y	364	40.6	62	35.4		81	18.8	236	59.3	109	44.9	***
Cultured	**Miss/Unk**	205	22.9	71	40.6		89	20.6	86	21.6	101	41.6	
	None	292	32.6	41	23.4		219	50.8	92	23.1	22	9.1	
	Islets cultured >=6 hrs	400	44.6	63	36.0		123	28.5	220	55.3	120	49.4	***
Gradient type	**Miss/Unk**	184	20.5	34	19.4		89	20.6	42	10.6	87	35.8	
	None	1	0.1	-	0.0		1	0.2	-	0.0	-	0.0	
	Mixed	13	1.4	3	1.7		3	0.7	11	2.8	2	0.8	
	Discontinuous	34	3.8	18	10.3		30	7.0	21	5.3	1	0.4	
	Continuous	599	66.8	115	65.7		266	61.7	302	75.9	146	60.1	
	Both	66	7.4	5	2.9		42	9.7	22	5.5	7	2.9	

* = p <.05; ** = p <.01; *** = p <.001

The use of UW solution and 2-layer has declined over the decade, while the use of other types has increased.

Many more islets were cultured in the recent era than in the early part of the decade.

More ITA preparations were cultured then IAK/SIK.

The use of Pulmozyme has increased over the decade.

Exhibit 3-1B
Pancreas Digestion Combinations Involving Thermolysin/Pulmozyme

	Thermolysin	Pulmozyme
	N	N
Collagenase P	1	9
Liberase	7	274
Serva/NB1	-	97
Sigmablend	-	2
Collagenase: other	59	55

In several instances, more than one primary enzyme was used in conjunction with thermolysin or pulmozyme; hence, the totals are higher than in the previous table.

Exhibit 3-1C
Final Islet Preparation Microbiology (Positive)

Final islet preparations for infusion	Transplant type					Era						
	ITA		IAK/SIK		p	1999-2003		2004-2006		2007-2009		p
	N	%	N	%		N	%	N	%	N	%	
Gram stain	0	-	0	-		0	-	0	-	0	-	
Aerobic culture	13	1.4	3	1.7		7	1.6	3	0.8	6	2.5	
Anaerobic culture	5	0.6	-	0.0		4	0.9	1	0.3	-	0.0	
Fungal Culture	4	0.4	1	0.6		-	0.0	4	1.0	1	0.4	
Mycoplasma	1	0.1	-	0.0		1	0.2	-	0.0	-	0.0	

Exhibit 3-2
Cold Ischemia Information

	Transplant type						p	Era									p
	ITA			IAK/SIK				1999-2003			2004-2006			2007-2009			
	N	Mean	SD	N	Mean	SD		N	Mean	SD	N	Mean	SD	N	Mean	SD	
Time from cross clamp to pancreas recovery (mins)	500	0.8	1.3	131	0.9	0.4		220	0.6	0.5	285	0.9	1.5	126	0.8	0.9	
Duration of cold ischemia (hrs)	671	7.4	3.4	124	6.4	2.8	**	343	7.0	3.2	319	7.4	3.3	133	7.4	3.9	*
Time from brain death to pancreas recovery (hrs)	453	19.4	8.6	120	16.1	10.1	***	210	16.8	7.8	251	19.2	9.3	112	21.1	9.7	***
Culture time (hrs)	692	17.1	18.6	104	17.0	18.3		342	11.7	17.9	312	18.9	17.3	142	26.3	18.6	***

* = p <.05; ** = p <.01; *** = p <.001

Mean duration of cold storage was about 1 hour longer for ITA than IAK.

Mean time from brain death to pancreas recovery was about 3 hours longer for ITA than IAK, and has increased over the decade by 5 hours.

Mean culture time has increased over the decade by more than 15 hours, including an increasing proportion of preparations being cultured at all.

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Exhibit 3-4A
Islet Product Characteristics

Final islet preparation for infusion	Transplant type							Era									
	ITA			IAK/SIK			p	1999-2003			2004-2006			2007-2009			p
	N	Mean	SE	N	Mean	SE		N	Mean	SE	N	Mean	SE	N	Mean	SE	
Total cell volume	693	3.9	0.1	104	4.4	0.3	*	337	3.9	0.1	321	4.0	0.1	139	4.0	0.2	
Total islet particles (final preparation)	615	400.9	6.8	126	410.4	16.8		315	410.2	9.7	281	414.0	10.7	145	363.8	12.5	
Embedded islets (%)	503	17.0	0.9	35	18.7	3.1		213	15.7	1.3	208	18.0	1.5	117	18.1	1.9	
IEQs infused	774	427.0	5.6	150	397.6	11.8	*	371	417.4	7.5	367	419.9	8.6	186	436.4	11.2	
Islet equivalents (1000s) / kg donor weight	744	5.0	0.1	144	4.9	0.1		358	5.1	0.1	356	5.0	0.1	174	4.8	0.1	*
Beta cells (1000s)	251	227.8	12.0	22	330.9	40.4	*	137	217.0	17.2	97	223.2	16.4	39	335.2	32.2	***
Beta cells (1000s) / kg donor weight	243	2.9	0.2	22	4.1	0.5		129	2.9	0.3	97	2.9	0.2	39	3.9	0.4	*
Insulin content (micrograms)	247	3.5	0.1	28	3.0	0.4		156	3.3	0.2	117	3.7	0.2	2	1.7	0.3	
Total endotoxin units	588	22.7	2.3	97	23.7	4.4		268	24.1	3.2	287	28.5	3.8	130	7.6	2.4	**
Endotoxin units / kg donor weight	573	0.3	0.0	92	0.3	0.1		257	0.3	0.0	284	0.3	0.0	124	0.1	0.0	***
Islet potency: Stimulation index	620	3.3	0.1	107	2.6	0.2		315	3.4	0.2	283	3.2	0.2	129	2.6	0.2	***
Islet viability	644	90.8	0.3	125	91.6	0.5		286	91.2	0.4	325	91.3	0.3	158	89.8	0.5	
Purity	653	62.2	0.7	139	57.6	1.7	**	306	60.4	1.1	341	61.3	1.0	145	63.5	1.4	*
Total DNA	294	9.4	0.6	29	9.0	1.8		155	8.3	0.9	126	9.1	0.8	42	14.2	1.3	***

* = p <.05; ** = p <.01; *** = p <.001

IEQs/kg has decreased over the decade while total IEQs has not changed; hence, the drop in IEQs/kg is due to the increase in donor weight over the decade (See Exhibit 2-11).

Total Beta cells and β-cells/kg were higher for IAK/SIK and have increased over the decade.

Endotoxin (both total and /kg) has declined sharply in the last 3 years.

Stimulation index was higher for ITA and has declined over the decade.

Exhibit 3-4B
Islet Product Characteristics by Infusion Sequence

Transplant type ITA										
	Infusion Number									
	1			2			>=3			
	N	Mean	SE	N	Mean	SE	N	Mean	SE	p
Total cell volume	349	4.1	0.1	251	3.8	0.1	93	3.4	0.2	***
Total islet particles (final preparation)	300	416.8	10.1	230	394.0	10.9	85	364.0	15.6	*
Embedded islets (%)	242	15.7	1.2	189	18.1	1.6	72	18.6	2.7	
IEQs infused	401	443.0	7.8	278	409.2	9.5	95	411.2	15.2	**
Islet equivalents (1000s) / kg donor weight	385	5.1	0.1	269	4.8	0.1	90	4.9	0.2	
Beta cells (1000s)	120	234.6	19.4	98	224.5	17.7	33	212.7	25.1	
Beta cells (1000s) / kg donor weight	117	3.1	0.4	95	2.8	0.2	31	2.8	0.3	
Insulin content (micrograms)	129	3.6	0.2	96	3.2	0.2	22	4.1	0.4	
Total endotoxin units	293	19.4	2.4	213	25.2	4.5	82	28.0	8.0	
Endotoxin units / kg donor weight	285	0.2	0.0	209	0.3	0.1	79	0.3	0.1	
Islet potency: Stimulation index	311	3.4	0.2	225	3.5	0.3	84	2.6	0.3	
Islet viability	319	90.9	0.3	233	90.9	0.4	92	90.0	0.8	
Purity	323	62.2	1.0	239	61.2	1.2	91	64.7	1.9	
Total DNA	141	9.9	1.0	114	8.9	0.8	39	9.3	1.2	

* = p <.05; ** = p <.01; *** = p <.001

Total cell volume and total islet particles have decreased with subsequent infusions, while endotoxin/kg has increased with subsequent infusions.

Exhibit 3-4B
Islet Product Characteristics by Infusion Sequence

Transplant type IAK/SIK										
Final Islet Preparations for Infusion	Infusion Number									p
	1			2			>=3			
	N	Mean	SE	N	Mean	SE	N	Mean	SE	
Total cell volume	49	4.5	0.4	42	4.3	0.4	13	4.5	0.3	
Total islet particles (final preparation)	60	440.4	27.7	45	382.1	25.3	21	385.2	29.8	
Embedded islets (%)	19	18.7	4.2	12	12.7	4.3	4	37.0	9.4	
IEQs infused	75	423.6	17.5	56	376.4	18.3	19	357.7	29.4	**
Islet equivalents (1000s) / kg donor weight	73	5.1	0.2	53	4.6	0.2	18	5.0	0.5	
Beta cells (1000s)	9	348.2	74.4	9	334.6	47.3	4	283.5	123.5	
Beta cells (1000s) / kg donor weight	9	4.1	0.8	9	4.3	0.6	4	3.7	1.7	
Insulin content (micrograms)	10	3.4	0.5	12	3.1	0.7	6	2.2	0.5	
Total endotoxin units	49	22.8	5.1	34	28.0	8.9	14	16.7	12.1	
Endotoxin units / kg donor weight	46	0.2	0.1	32	0.3	0.1	14	0.2	0.2	
Islet potency: Stimulation index	51	2.7	0.3	41	2.5	0.4	15	2.2	0.4	
Islet viability	59	91.5	0.8	47	92.3	0.8	19	90.3	1.4	
Purity	69	57.8	2.3	50	59.0	2.6	20	53.6	5.4	
Total DNA	12	8.4	2.7	12	10.6	3.5	5	6.9	2.6	

* = p <.05; ** = p <.01; *** = p <.001

For IAK/SIK, total IEQs infused per preparation has declined with subsequent infusion sequence.

Exhibit 3-5
Islet Characteristics by Pancreas Preservation Method

Final Islet Preparations for Infusion	Pancreas Preservation Method																		p
	UW only			2L only			HTK only			Celsior			UW+2L			Other			
	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	
Total cell volume	382	4.0	0.1	198	3.7	0.1	71	3.8	0.2	19	3.7	0.4	35	4.2	0.4	68	4.1	0.3	
Total islet particles (final preparation)	361	402.8	8.5	167	365.7	12.7	76	406.3	14.8	20	361.5	33.9	37	**449.8**	**33.3**	57	457.9	29.2	*
Embedded islets (%)	253	16.0	1.2	111	18.6	2.1	83	17.0	2.2	17	14.5	3.9	22	23.9	5.0	44	14.0	2.8	
IEQs infused	420	427.3	7.8	206	415.1	11.2	72	439.9	16.7	20	317.2	12.9	38	496.2	26.7	142	405.6	10.3	
Islet equivalents (1000s) / kg donor weight	408	5.1	0.1	206	4.8	0.1	69	4.9	0.2	20	4.0	0.2	38	6.1	0.4	122	4.9	0.1	
Beta cells (1000s)	144	196.5	15.4	76	255.1	21.9	40	**329.4**	**31.8**	0	-	-	7	241.1	58.6	6	**316.3**	**33.7**	**
Beta cells (1000s) / kg donor weight	136	2.8	0.3	76	3.0	0.2	40	3.8	0.4	0	-	-	7	3.2	0.6	6	3.2	0.4	
Insulin content (micrograms)	170	3.4	0.2	81	3.4	0.2	3	5.7	1.2	0	-	-	9	5.1	0.9	12	2.9	0.5	
Total endotoxin units	339	25.3	3.2	166	28.9	4.0	86	4.4	2.3	6	0.2	0.1	32	45.4	16.6	41	8.4	4.5	
Endotoxin units / kg donor weight	328	0.3	0.0	166	0.3	0.0	83	0.0	0.0	6	0.0	0.0	32	0.6	0.2	36	0.1	0.0	
Islet potency: Stimulation index	385	**3.4**	**0.2**	176	**3.1**	**0.2**	**80**	2.8	0.3	6	1.7	0.4	30	**3.1**	**0.6**	41	2.5	0.3	*
Islet viability	362	91.0	0.3	200	92.4	0.4	88	87.7	0.7	11	88.9	1.2	36	91.4	0.9	55	90.6	0.8	
Purity	364	**63.2**	**1.0**	201	**61.6**	**1.2**	**83**	63.9	1.7	18	47.3	3.9	38	**63.9**	**3.0**	62	55.5	2.3	**
Total DNA	178	7.5	0.7	85	11.7	1.3	41	**13.7**	**1.2**	1	12.3	-	13	7.5	1.6	5	8.2	1.3	*

* = p <.05; ** = p <.01; *** = p <.001

UW + 2L yielded the highest total islet particles.

UW, 2L and their combination yielded the highest stimulation index and purity.

HTK yielded the highest total beta cells and total DNA.

Exhibit 3-6
Relationship between (Categorical) Islet Predictors and Final Islet Product Characteristics
(See Online Supplement for details)

p<0.05: (See Appendix C for details)	Islet characteristics													
	Packed cell volume	Total particle count	Trapped islets	Total IEQs infused	IEQs/kg donor	Total beta cells	Beta cells/kg donor	Insulin content	Total endotoxin	Endotoxin/ kg donor	Stimulation index	Viability	Purity	DNA content
Islet predictors														
ITA vs. IAK/SIK	0.02			0.04		0.02					0.02		0.008	
Year						<.001	0.02		0.002	<.001		0.04	0.02	
Donor gender		0.004		0.006	0.001									
Donor blood type A	0.03		0.04		0.01			0.02						
Donor CMV									0.01	0.02				
Donor Hx HPT				0.03					0.03	0.02				
Donor Hx ETOH												0.03		
Donor hospital transfusion														
Donor intra-op transfusion				0.04	0.006									
Donor given steroid				<0.001	0.005	0.004	0.02	0.01	<.001	<.001			<.001	
Donor given insulin				<0.001		<.001	0.001					0.04	0.02	
Procurement team related				<0.001	0.04				0.01	0.02	0.03	0.01		
Pancreas preservation		0.01				0.001					0.04		0.005	
Pulmozyme	0.003	0.002			0.003			0.03			0.006	0.003		
Thermolysin												0.004		
Gradient type	0.,01		0.02	0.03		0.002	0.001			0.02			<.001	0.001

Exhibit 3-7
Significant Correlations (p<0.05) between Islet Product Characteristics and (Continuous) Predictors

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	pckclvol_c	*totparticles_c*	*tottrap_c*	*ieqinf_c*	*ieqkg*	*totalbeta_c*	*totalbetakg_c*	*totalinsulin_c*
Mean donor age (yrs)	-0.09516	0.05401	-0.17864	-0.06109	0.02329	-0.09969	-0.14094	0.08775
	0.0137	0.1792	0.0001	0.0941	0.5279	0.1196	0.0277	0.1718
	670	620	463	752	737	245	244	244
Donor Weight (kg)	0.06107	0.04536	-0.07157	**0.32900**	**-0.29201**	0.05776	**-0.25973**	-0.00308
	0.0891	0.2245	0.1024	**<.0001**	**<.0001**	0.3489	**<.0001**	0.9601
	776	719	522	**888**	**888**	265	**265**	267
Donor height	0.05501	0.08524	-0.04185	0.11447	-0.17111	-0.06875	-0.24963	0.04436
	0.1243	0.0213	0.3376	0.0006	<.0001	0.2657	<.0001	0.4712
	782	729	527	897	886	264	264	266
Donor Body Mass Index (kg/m2)	0.02199	-0.00496	-0.07959	**0.28784**	**-0.24073**	0.09253	-0.17585	-0.02225
	0.5413	0.8945	0.0698	**<.0001**	**<.0001**	0.1337	0.0042	0.7179
	774	717	520	**886**	**886**	264	264	266
Pre-ins donor glucose	0.06521	0.02506	0.04663	0.01146	0.04834	-0.06555	0.02326	-0.00061
	0.1037	0.5523	0.3541	0.7644	0.2104	0.3244	0.7315	0.9923
	624	565	397	687	673	228	220	251
Max donor glucose	0.03510	-0.05243	-0.05905	0.11042	0.09258	0.05525	0.04571	-0.07747
	0.3788	0.2126	0.2405	0.0032	0.0144	0.4257	0.5173	0.2626
	631	567	397	710	698	210	203	211
Donor creatinine	0.04436	-0.01208	-0.05091	0.09807	-0.02751	0.08057	-0.02639	-0.09918
	0.2516	0.7661	0.2997	0.0075	0.4562	0.2730	0.7199	0.1757
	670	609	417	743	736	187	187	188
Donor BUN	0.10412	-0.02981	0.00227	0.09758	-0.01304	0.05823	0.03472	-0.00341
	0.0214	0.5444	0.9729	0.0233	0.7632	0.5731	0.7370	0.9698
	488	416	226	540	536	96	96	126
Donor bilirubin	0.01400	0.01307	0.07985	0.09526	0.00205	0.05840	0.04769	0.16287
	0.7407	0.7729	0.1642	0.0186	0.9599	0.5143	0.5944	0.0673
	561	490	305	610	605	127	127	127
Donor AST	0.01400	-0.03142	-0.05872	0.01720	0.00166	0.01478	-0.00620	0.04774
	0.7367	0.4781	0.2950	0.6660	0.9671	0.8685	0.9447	0.5882
	579	512	320	632	620	128	128	131

The only significant association between donor characteristics and islet product criteria was that higher donor weight or BMI predicts higher IEQ yield.

Exhibit 3-7
Significant Correlations (p<0.05) between Islet Product Characteristics and (Continuous) Predictors

	Pearson Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations							
	pckclvol_c	*totparticles_c*	*tottrap_c*	*ieqinf_c*	*ieqkg*	*totalbeta_c*	*totalbetakg_c*	*totalinsulin_c*
Donor ALT	0.01352 0.7455 579	-0.01933 0.6616 515	-0.06881 0.2175 323	0.02818 0.4713 656	0.00838 0.8317 645	0.11926 0.1715 133	0.06270 0.4734 133	0.03073 0.7245 134
Donor lipase	-0.01122 0.7905 563	0.00663 0.8829 495	-0.06838 0.2025 349	0.02126 0.6003 610	-0.00792 0.8459 605	-0.10933 0.1418 182	-0.10888 0.1445 181	-0.02184 0.7661 188
Donor serum amylase	-0.05240 0.1808 654	-0.04118 0.3156 596	0.00177 0.9714 411	-0.01663 0.6587 708	-0.04832 0.2010 702	-0.11343 0.1252 184	-0.06880 0.3534 184	-0.00850 0.9069 192
Time from cross clamp to pancreas recovery (mins)	0.01391 0.7486 533	0.02219 0.6238 491	0.08569 0.1164 337	-0.08907 0.0298 595	-0.04238 0.3057 586	0.13772 0.0602 187	0.08856 0.2281 187	-0.02335 0.7543 182
Time from brain death to pancreas recovery (hrs)	0.02383 0.6013 483	-0.08307 0.0828 437	-0.07695 0.1860 297	0.09923 0.0210 541	-0.04058 0.3498 533	0.18307 0.0144 178	0.05418 0.4726 178	-0.08368 0.2779 170
Cold ischemic time (hrs)	-0.10150 0.0071 702	0.08611 0.0274 656	-0.03109 0.5051 462	0.00692 0.8503 747	0.01464 0.6928 731	-0.06203 0.3135 266	-0.05193 0.4062 258	0.04449 0.4674 269
Culture time (hrs)	-0.12170 0.0012 705	-0.02631 0.5025 652	0.06967 0.1247 487	0.02896 0.4291 748	-0.01021 0.7823 735	**0.31024** **<.0001** **266**	0.18012 0.0033 265	-0.09375 0.1251 269
Donor lipase	-0.01122 0.7905 563	0.00663 0.8829 495	-0.06838 0.2025 349	0.02126 0.6003 610	-0.00792 0.8459 605	-0.10933 0.1418 182	-0.10888 0.1445 181	-0.02184 0.7661 188
Donor serum amylase	-0.05240 0.1808 654	-0.04118 0.3156 596	0.00177 0.9714 411	-0.01663 0.6587 708	-0.04832 0.2010 702	-0.11343 0.1252 184	-0.06880 0.3534 184	-0.00850 0.9069 192

Exhibit 3-7
Significant Correlations (p<0.05) between Islet Product Characteristics and (Continuous) Predictors

	Pearson Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations							
	pckclvol_c	*totparticles_c*	*tottrap_c*	*ieqinf_c*	*ieqkg*	*totalbeta_c*	*totalbetakg_c*	*totalinsulin_c*
Time from cross clamp to pancreas recovery (mins)	0.01391 0.7486 533	0.02219 0.6238 491	0.08569 0.1164 337	-0.08907 0.0298 595	-0.04238 0.3057 586	0.13772 0.0602 187	0.08856 0.2281 187	-0.02335 0.7543 182
Time from brain death to pancreas recovery (hrs)	0.02383 0.6013 483	-0.08307 0.0828 437	-0.07695 0.1860 297	0.09923 0.0210 541	-0.04058 0.3498 533	0.18307 0.0144 178	0.05418 0.4726 178	-0.08368 0.2779 170
Cold ischemic time (hrs)	-0.10150 0.0071 702	0.08611 0.0274 656	-0.03109 0.5051 462	0.00692 0.8503 747	0.01464 0.6928 731	-0.06203 0.3135 266	-0.05193 0.4062 258	0.04449 0.4674 269
Culture time (hrs)	-0.12170 0.0012 705	-0.02631 0.5025 652	0.06967 0.1247 487	0.02896 0.4291 748	-0.01021 0.7823 735	**0.31024** **<.0001** **266**	0.18012 0.0033 265	-0.09375 0.1251 269

	Pearson Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations					
	totalendo_c	*totendokg_c*	*isstimin_mean_c*	*iptviab_mean_c*	*purity_c*	*totaldna_c*
Mean donor age (yrs)	0.00843 0.8350 613	0.02338 0.5667 603	-0.15184 <.0001 660	-0.10366 0.0068 681	0.00760 0.8451 663	-0.11765 0.0468 286
Donor Weight (kg)	0.09739 0.0120 665	-0.00121 0.9752 665	0.03003 0.4250 708	0.08331 0.0227 748	0.11986 0.0009 770	-0.02271 0.6886 314
Donor height	-0.03882 0.3138 675	-0.05977 0.1236 665	0.04520 0.2278 714	0.08904 0.0141 759	0.03408 0.3415 781	-0.04206 0.4584 313
Donor Body Mass Index (kg/m2)	0.12634 0.0011 665	0.03203 0.4096 665	0.00270 0.9429 707	0.04506 0.2183 748	0.10818 0.0027 769	-0.03011 0.5956 313
Pre-ins donor glucose	0.08598 0.0427 556	0.09765 0.0229 543	0.01094 0.7873 610	-0.05996 0.1333 628	-0.00072 0.9858 623	0.07480 0.2223 268
Max donor glucose	0.09181 0.0268 582	0.08916 0.0332 571	0.00517 0.8992 603	0.11510 0.0031 660	0.07728 0.0479 656	-0.03154 0.6183 252

Exhibit 3-7
Significant Correlations (p<0.05) between Islet Product Characteristics and (Continuous) Predictors

	Pearson Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations					
	totalendo_c	*totendokg_c*	*isstimin_mean_c*	*iptviab_mean_c*	*purity_c*	*totaldna_c*
Donor creatinine	-0.01904 0.6385 611	-0.02644 0.5166 604	0.02121 0.6005 612	0.01426 0.7088 688	-0.00317 0.9326 713	0.09434 0.1502 234
Donor BUN	-0.03605 0.4336 474	-0.03372 0.4658 470	0.06302 0.1703 475	0.06289 0.1452 538	-0.03173 0.4647 533	-0.00815 0.9244 138
Donor bilirubin	0.03567 0.4151 524	0.02190 0.6186 519	0.05099 0.2444 523	-0.00431 0.9163 597	0.04810 0.2367 607	-0.03399 0.6570 173
Donor AST	-0.00217 0.9595 549	-0.01279 0.7672 538	-0.01806 0.6734 547	-0.00098 0.9806 621	-0.04574 0.2528 627	0.00895 0.9067 174
Donor ALT	-0.00876 0.8371 553	-0.01473 0.7319 543	0.00038 0.9930 552	-0.01181 0.7683 625	-0.03536 0.3760 629	0.03308 0.6602 179
Donor lipase	0.02782 0.5181 542	0.01606 0.7098 539	-0.05394 0.2016 562	0.10451 0.0104 600	0.03588 0.3904 575	0.02517 0.7092 222
Donor serum amylase	0.05127 0.2156 585	0.04597 0.2690 580	-0.02975 0.4674 599	0.03778 0.3318 662	0.02998 0.4351 680	-0.08544 0.1977 229
Time from cross clamp to pancreas recovery (mins)	-0.06173 0.1783 477	-0.06217 0.1789 469	0.00090 0.9839 500	-0.01325 0.7579 544	-0.09400 0.0265 557	0.08456 0.2180 214
Time from brain death to pancreas recovery (hrs)	0.10824 0.0211 454	0.10247 0.0303 447	0.02880 0.5317 474	0.00130 0.9767 511	0.18525 <.0001 502	0.06108 0.3902 200
Cold ischemic time (hrs)	-0.03745 0.3465 634	-0.03606 0.3700 620	0.00137 0.9716 681	-0.11237 0.0030 695	0.03353 0.3809 685	-0.04421 0.4402 307
Culture time (hrs)	0.11926 0.0029 621	0.12150 0.0026 610	0.01608 0.6816 653	-0.07117 0.0627 685	0.11201 0.0031 696	**0.29439** **<.0001** **313**

Chapter 4
Immunosuppression and Other Medications

Introduction

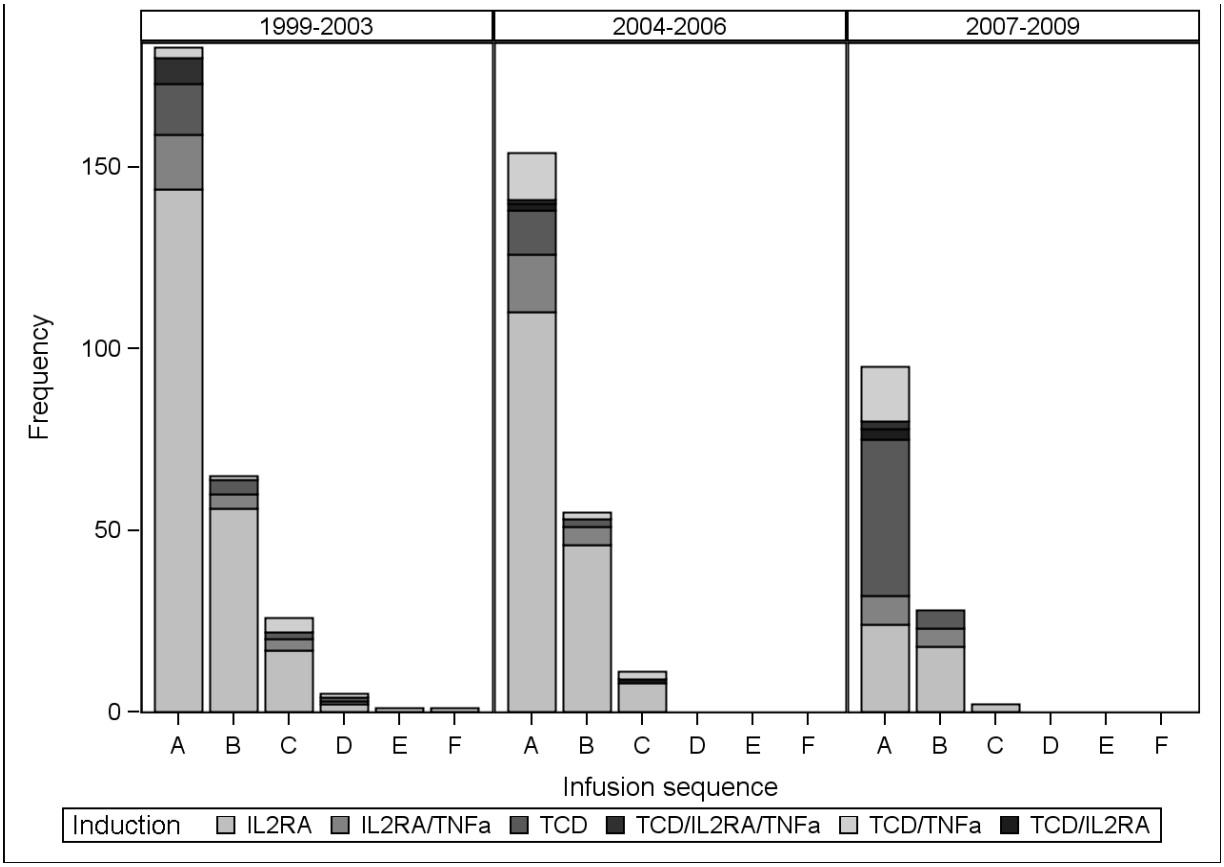
The following table classifies the induction and maintenance therapies used in CITR allograft recipients.

Super category	Category	Agent
Tcell depleting agent	Monoclonal TCD	Alemtuzumab (Campath)
	Monoclonal antiCD3	Teplizumab (hOKT3y-1-ala-ala)
	Polyclonal TCD	Antithymocyte
		Antilymphocyte globulin
Tcell Activation inhibition	IL2R antagonist	Daclizumab
		Basiliximab
Replication inhibition	DNA analogue	Azathioprine
	IMPDH inhibitor	Mycophenolate Mofetil/ Mycophenolic acid
	mTor inhibitor	Sirolimus
		Everolimus
Lymphocyte tracking inhibitor	LFA1 inhibitor	Efalizumab (Raptiva)
Desensitization	Immunoglobulin	IVIG
Co-Stimulation Inhibition	Monoclonal antiCD28	Belatacept/Abatacept
Calcineurin inhibitor	Calcineurin inhibitor	Cyclosporine
		Neoral
		Tacrolimus
Bcell Depleting	Bcell Depleting	Rituximab
Anti-inflammatory	Corticosteroids	Steroid
	IL1 Receptor antagonist (IL1RA)	IL1R
		Deoxyspergualin
	TNF antagonist (TNF-a inhibitor)	Infliximab
		Etanercept

Multiple induction and maintenance agents may have been administered peri- and post- several infusions in the same recipient. In displays of results post last infusion, the cumulated induction agents are classified into the appropriate class combination (e.g., TCD+IL2RA – these could have been given at the same or different infusions in the recipient). For analysis of outcomes post infusion, the induction agents are cumulated and the resulting combination is carried forward through the patient's follow-up. Maintenance agents, categories and category combinations are computed at each follow-up time point post infusion. Hence, displays of maintenance combinations at any given time point, e.g., bar charts in Chapter 5, count the observation in the appropriate immunosuppression category at that time point, hence they are treated dynamically instead of statically as in a cohort.

Exhibit 4-1
Immunosuppression by Transplant Type, Era and Follow-up

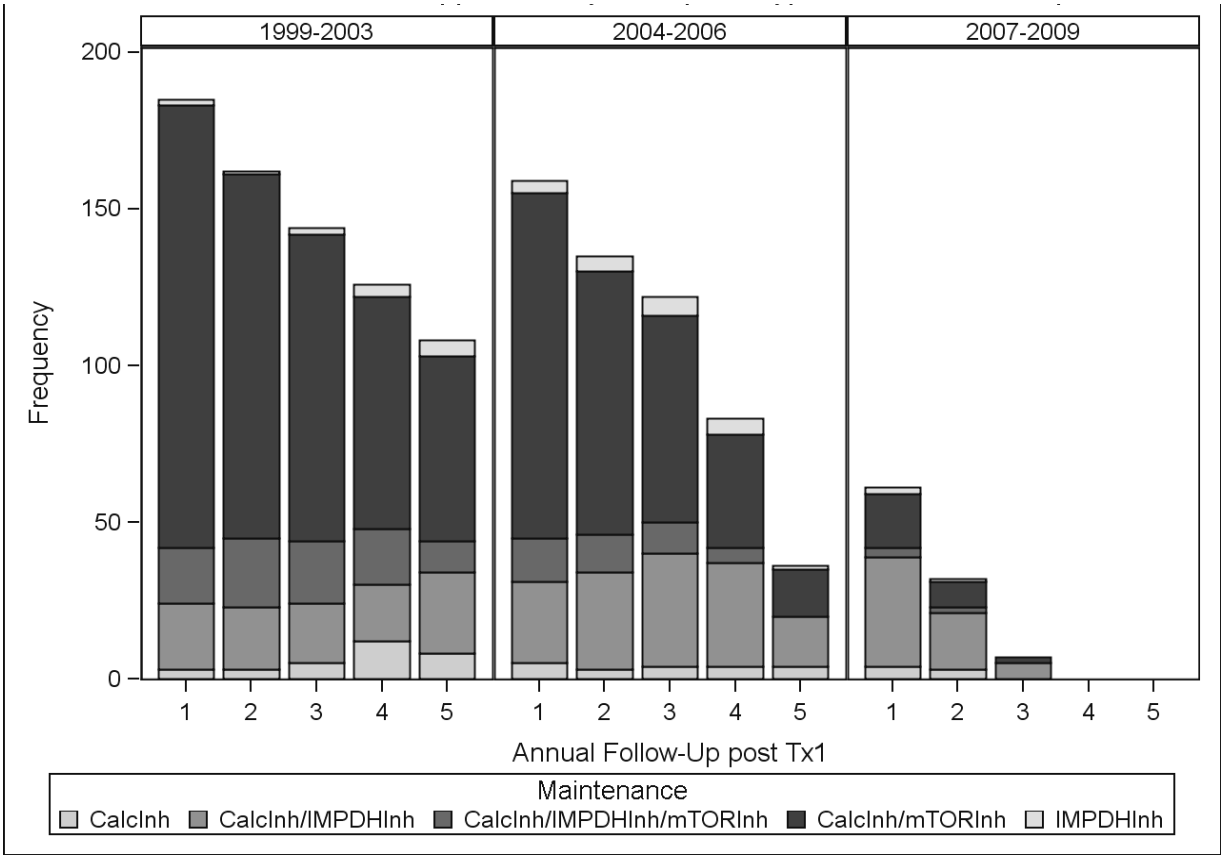
A. Induction at Tx1	Transplant type				Era					
	ITA		IAK/SIK		1999-2003		2004-2006		2007-2009	
	N	%	N	%	N	%	N	%	N	%
Missing	*83*	*19*	*4*	*5*	*30*	*14*	*30*	*16*	*27*	*22*
IL2RA	212	49	66	76	144	68	110	60	24	20
IL2RA/TNFa	32	7	7	8	15	7	16	9	8	7
TCD	64	15	5	6	14	7	12	7	43	35
TCD/IL2RA	3	1	2	2	.	.	2	1	3	2
TCD/IL2RA/TNFa	10	2	.	.	7	3	1	1	2	2
TCD/TNFa	28	6	3	3	3	1	13	7	15	12



This display shows the induction combination given at each infusion (A=1, B=2, etc.). Induction with IL2RA only prevailed in 1999-2003 and has been replaced in great part by T-cell depletion with or without TNFa inhibition or with IL2RA in the recent era and at subsequent re-infusion in all eras.

Exhibit 4-1
Immunosuppression by Transplant Type, Era and Follow-up, (continued)

B. Maintenance	Annual Follow-Up post Tx1											
	0		1		2		3		4		5	
	N	%	N	%	N	%	N	%	N	%	N	%
Missing	*31*	*6*	*25*	*6*	*20*	*6*	*19*	*7*	*11*	*5*	*8*	*5*
CalcInh	6	1	12	3	9	3	9	3	16	7	12	8
CalcInh/IMPDHInh	89	17	82	19	69	20	60	21	51	23	42	28
CalcInh/IMPDHInh/mTORInh	18	3	35	8	36	10	30	10	23	10	10	7
CalcInh/mTORInh	362	70	268	62	208	60	166	57	110	50	74	49
IMPDHInh	13	3	8	2	7	2	8	3	9	4	6	4



This display shows the number of recipients on the specified combination maintenance at each follow-up time point within each transplant era. A Calcineurin inhibitor+mTOR inhibitor regimen ("Edmonton protocol") comprised the abundant majority (~70%) of maintenance immunosuppression in the early era 1999-2003. Increasingly it has been replaced with a switch from the mTOR inhibitor to an IMPDH inhibitor in the recent era and in 4-5 year follow-up in all eras.

Exhibit 4-2
Biologic Agents Used Peri-Infusion

All infusions		Type				Era						Infusion Sequence											
		ITA		IAK/SIK		1999-2003		2004-2006		2007-2009		A		B		C		D		E		F	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
TCD	Alemtuz	16	1.9	.	.	1	0.2	9	2.5	6	3.0	14	2.7	2	0.6	.	.	.	.	.	.	.	.
	ACD3/hOKT3	9	1.1	.	.	4	0.9	2	0.6	3	1.5	9	1.7	.	.	.	.	.	.	.	.	.	.
	ATG	104	12.4	11	6.5	32	7.2	24	6.6	59	29.5	92	17.7	12	3.3	9	7.8	2	20.0	.	.	.	.
IL2-RA	Dacliz	356	42.4	89	53.0	235	52.8	167	46.0	43	21.5	299	57.6	114	31.5	29	25.2	3	30.0	.	.	.	.
	Basilix	40	4.8	17	10.1	16	3.6	22	6.1	19	9.5	33	6.4	20	5.5	2	1.7	.	.	1	100.0	1	100.0
LFA1-i	Efaliz	9	1.1	.	.	.	.	.	.	9	4.5	7	1.3	2	0.6	.	.	.	.	.	.	.	.
ACD28	Belatacept	3	0.4	.	.	.	.	.	.	3	1.5	2	0.4	1	0.3	.	.	.	.	.	.	.	.
TNFa-Blk	Infliximab	14	1.7	3	1.8	17	3.8	.	.	.	.	16	3.1	1	0.3	.	.	.	.	.	.	.	.
	Etancercept	96	11.4	12	7.1	24	5.4	50	13.8	34	17.0	72	13.9	21	5.8	13	11.3	2	20.0	.	.	.	.

Exhibit 4-3
Immunosuppression Categories & Agents, by Transplant Type and Follow-up

Immunosuppression Post Infusion 1		Transplant Type													
		ITA							IAK/SIK						
		Years post Tx 1							Years post Tx 1						
		0	0.5	1	2	3	4	5	0	0.5	1	2	3	4	5
Total		432	391	357	288	237	185	128	87	80	73	61	55	35	24
Category	Specific Agent														
TCD Inh	Total	105	.	.	.	.	1	.	10	.	.	.	.	.	.
	Alemtuz	14	.	.	.	.	.	.	.	.	.	.	.	.	.
	ACD3/hOKT3	9	.	.	.	.	.	.	.	.	.	.	.	.	.
	ATG	82	.	.	.	.	1	.	10	.	.	.	.	.	.
IL2-RA Inh	Total	257	33	26	24	14	8	5	75	15	8	2	3	2	.
	Daclizumab	238	32	24	22	13	7	5	61	15	8	2	3	2	.
	Basiliximab	19	1	2	2	1	1	.	14	.	.	.	.	.	.
TNFa Blk	Total	78	4	3	2	.	2	.	10	1	.	.	.	.	.
	Infliximab	14	1	1	.	.	.	.	2	.	.	.	.	.	.
	Etanercept	64	3	2	2	.	2	.	8	1	.	.	.	.	.
BCD Inh															
ACD28	Belatacept	2	1	1	.	.	.	.	.	.	.	.	.	.	.
DNA-Anal	AZA	4	2	2	1	1	1	1	2	3	3	2	2	.	.
mTOR Inh	Total	356	321	284	221	178	119	74	54	53	47	40	34	25	17
	Sirolimus	350	315	280	218	176	118	73	52	51	46	39	33	24	16
	Everolimus	6	6	4	3	2	1	1	2	2	1	1	1	1	1
Calcin Inh	Total	390	353	324	262	212	166	115	85	78	73	60	53	34	23
	Cyclosporin	6	5	3	2	3	2	2	7	6	6	5	4	1	1
	Neoral	12	9	9	9	8	7	3	14	12	12	9	9	8	4
	Tacrolimus	372	339	312	251	201	157	110	67	62	57	48	42	26	18
IMPDH-Inh	MMF	88	111	113	100	85	73	53	40	28	29	24	22	12	7
LFA1-i	Efalizumab	7	6	4	1	.	.	.	.	.	.	.	.	.	.
IG	IV-IG	1	.	.	.	.	.	.	.	.	.	.	.	.	.
Steroid	Steroid	75	29	24	16	16	12	6	22	19	18	16	16	9	6
IL1-RA inh	Total	18	3	2	2	2	.	.	.	.	.	.	.	.	.
	DSG	2	.	.	.	.	.	.	.	.	.	.	.	.	.
	IL-1R	13	1	.	.	.	.	.	.	.	.	.	.	.	.

Chapter 5
Graft Function

INTRODUCTION

The main focus of this chapter is to describe the clinical success of islet transplantation and identify factors predictive of it, to both guide current practice and direct future research. Since the Edmonton era, there are now sufficient numbers of cases and sufficient long-term follow-up on alternative immunosuppressive strategies to reasonably allow preliminary identification of beneficial factors in addition to selection of recipients by favorable patient characteristics, previously identified in the CITR data and by individual site experiences.

While the CITR definition of insulin independence is simplistic (≥2 weeks), it is based on patient diaries, is verified at scheduled visits, and does represent the most completely available outcome data in the Registry, with fasting C-peptide also having reasonably complete reporting. As discussed in the methods section and Chapter 8, the data on the most recent years (2008-2009) is not sufficiently complete to validly contribute to a comprehensive investigation of impelling factors; analysis of the 2008-2009 data will have to wait until the data is sufficiently complete. Hence this chapter presents results on data from 1999-2007.

Salient results are presented in Chapter 5 Exhibits. Detailed results are available in supplements online at www.citregistry.org/Reports /AnnualReport /2010 /Supplements. The table on the following page relates the Chapter Exhibits to the Supplements.

Chapter 5 Supplemental Exhibit Map

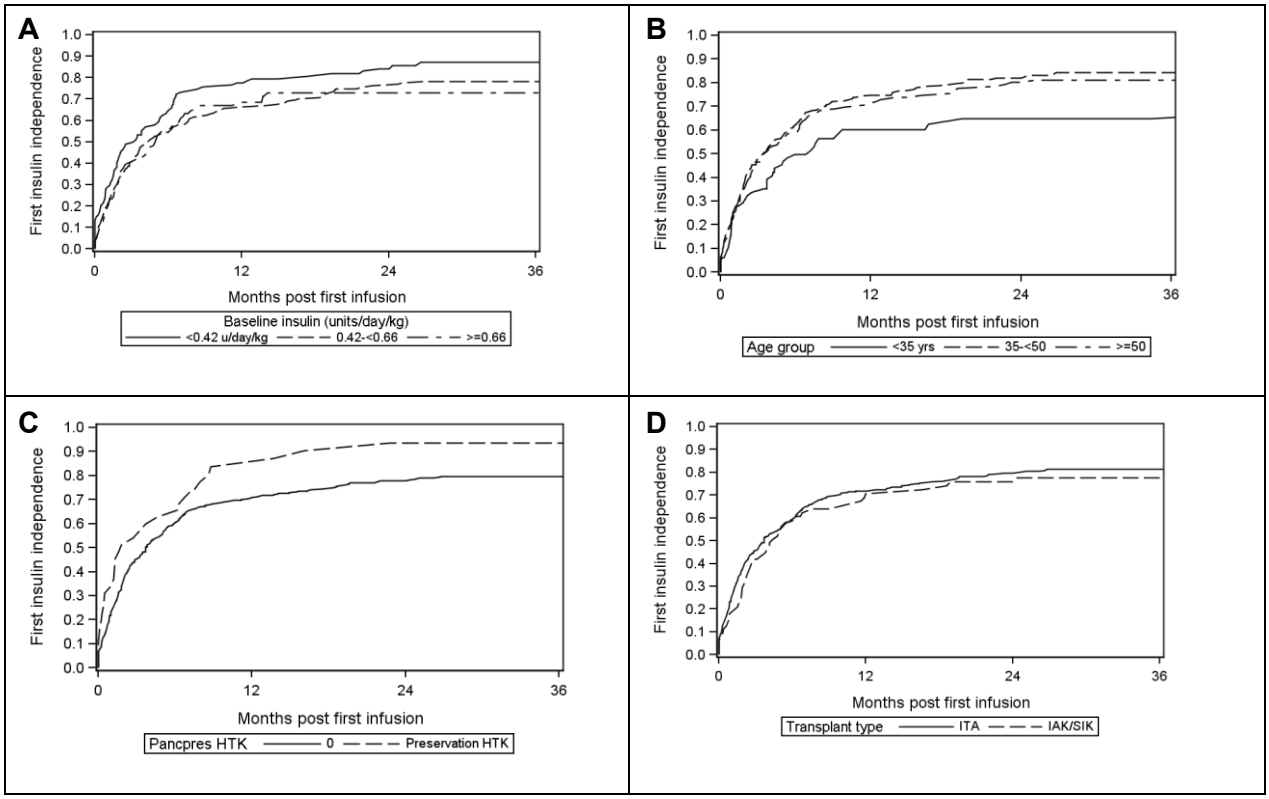
	Chapter 5 Exhibit	Supplemental Exhibit
Achievement of insulin independence, loss of insulin independence and complete graft failure post last infusion: Time to event analysis for all predictors univariately	-	A-1
Achievement of insulin independence post first infusion (Kaplan-Meiers)	5-1	-
Achievement of insulin independence post last infusion (Kaplan-Meiers)	5-2	A-2
Retention of insulin independence post last infusion (K-Ms)	5-3	A-3
Factors of primary endpoint prevalence post last infusion (Summary Table)		A-4 S
Insulin independence prevalence (bar charts)	5-4	A-4
Retention of C-peptide>=0.3 ng/mL post last infusion (K-Ms)	5-5	A-5
Fasting C-peptide>=0.3 ng/mL prevalence post last infusion (Bar charts)	-	A-6
Reinfusion (Bar charts and K-Ms)	5-6	-
Fasting blood glucose 60-140 mg/mL prevalence post last infusion (Bar charts)	5-7	A-7
HbA1c<6.5% or drop by 2% (bar charts)	5-8	A-8
Absence of severe hypoglycemia (bar charts)	5-9	A-9
Insulin dose post last infusion (Box plots)	5-10	A-10
Fasting C-peptide levels post last infusion (Box plots)	5-11	A-10
HbA1c levels post last infusion (Box plots)	5-12	A-10
Fasting blood glucose levels post last infusion (Box plots)	5-13	A-10
Univariate effect of predictors on prevalence of primary endpoints post last infusion (correspond to Supplements A-4, A-6, A-7, A-8 and A-9)	-	A-11
Association of C-peptide≥0.3 ng/dL on other primary outcomes	5-14	-
Insulin requirement by concurrent C-peptide level	5-15	-
Complications of diabetes post islet transplantation	5-16	-

RESULTS

Insulin independence

Achievement of insulin independence from initial islet infusion, with or without subsequent re-infusion, is an indicator of the rate of engraftment under the real-time conditions of competing events including early graft function or loss, islet resource availability for re-infusion, individual tolerance of immunossuppression, patient/doctor decisions and myriad other factors, some of which are characterized in the CITR data and others not. Notably, the cumulative rate of achievement of insulin independence (Exhibit 5-1) follows the general shape of engraftment curves for solid organs, but with a slower initial slope, indicative of multiple infusions. Importantly, favorable factors predict an 80-90% rate of ever achieving insulin independence with islet transplantation. Factors strongly predictive of first achievement of insulin independence were: lower baseline insulin requirement (Exhibit 5-1A, p=0.03), recipient age >35 years (Exhibit 5-1B, p=0.03), and pancreas preservation with HTK (Exhibit 5-1C, p=0.03). Notably, achievement of insulin independence did not vary by type of transplant (Exhibit 5-1D, p=0.34). These are univariate results without adjustment for other factors.

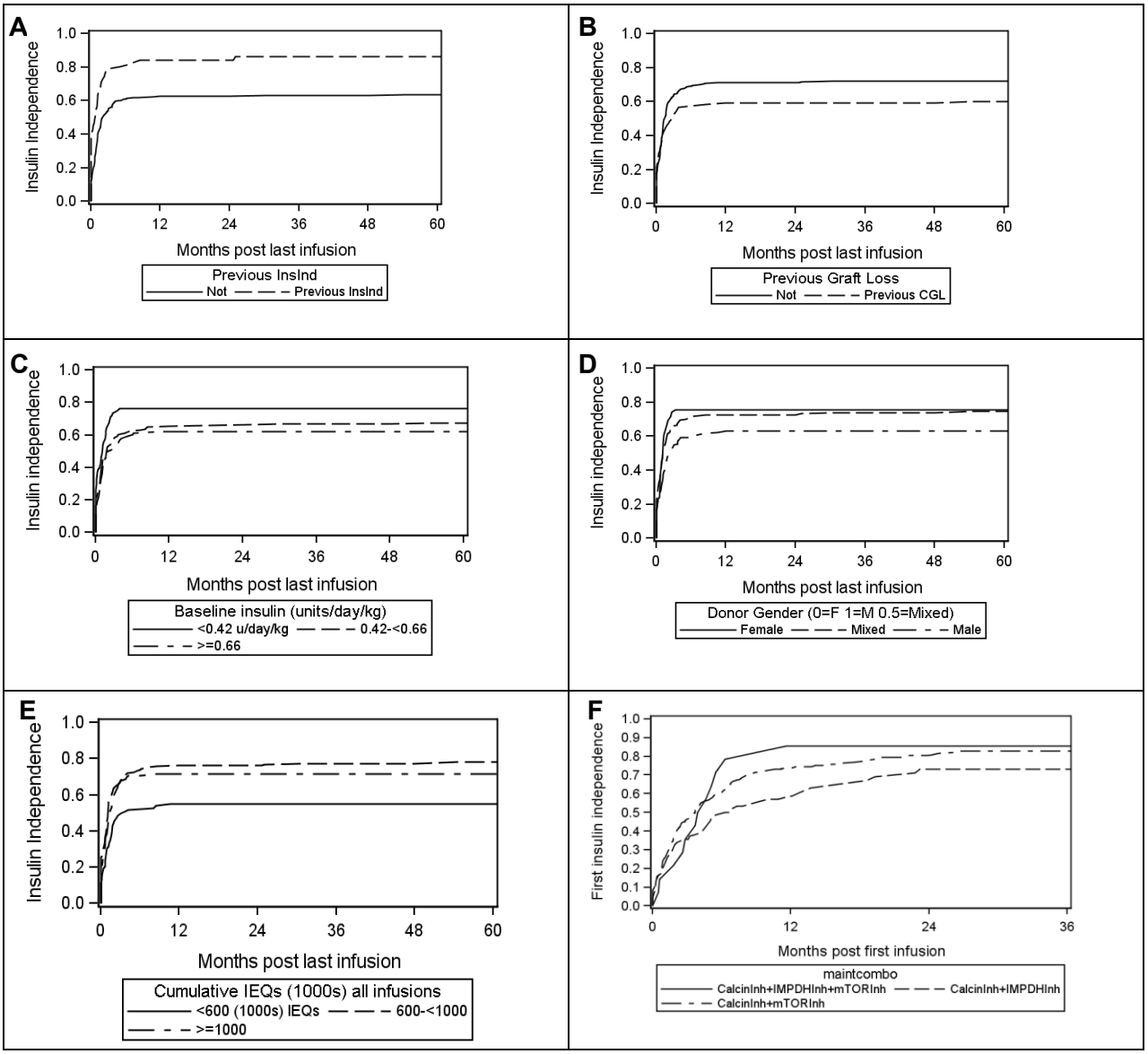
Exhibit 5-1
First Achievement of Insulin Independence Post First Infusion
(Regardless of total number of infusions; censored at final graft loss or end of follow-up)



Insulin independence (≥2 weeks) can be lost and re-achieved, making it difficult to analyze by any single method. While achievement and retention post last infusion ignore previous periods of insulin independence (as well as periods of dependence), they facilitate investigation of predictive factors. The cumulative event rates of achieving or re-achieving insulin independence post last infusion (Exhibit 5-2) rise quickly in contrast to post first infusion (Exhibit 5-1), due mostly to the fact that previously achieving insulin independence is a significant predictor or re-achieving it after re-infusion (Exhibit 5-2A, p<0.001).

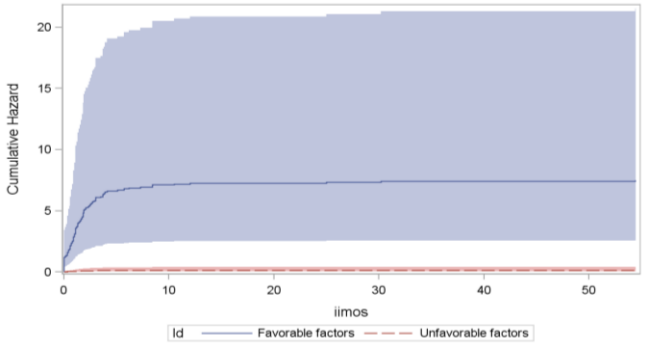
Complete graft loss (CGL) at an earlier infusion also predicts lower likelihood of achieving insulin independence on subsequent infusion (Exhibit 5-2B, p=0.05). Final factors from a multivariate model (Exhibit 5-2G) favorable for achieving insulin independence post last infusion include: baseline insulin requirement <0.42U/day/kg (Exhibit 5-2C, p=0.03), at least one female donor (Exhibit 5-2D, p=0.003), and IEQs >600 over all infusions (Exhibit 5-2E, p=0.003). The combination of the most favorable factors contrasted to the least favorable factors shows a wide separation of possible event rates (Exhibit 5-2H). While there is indication from this model that maintenance combinations with IMPDH inhibitors are favorable (Exhibit 5-2F, p=0.003), the effects of induction and maintenance immunosuppression agents prove difficult to isolate because they are given in combination, are changed across infusions and over follow-up time within the same patient, and the sample sizes with recent strategies are still relatively small (see Chapter 4). Furthermore, the emerging results yield unstable results for achievement vs. retention of insulin independence. With these constraints, additional or alternative approaches to assessing the effect of immunosuppression strategies are indicated, especially prevalence of insulin independence, which combines achievement and retention into an overall rate (see Exhibit 5-4).

Exhibit 5-2
Achievement of Insulin Independence Post Last Infusion
(Censored at final graft loss or end of follow-up)



G. Final multivariate model	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Baseline insulin (units/day/kg)	1	-0.19360	0.09169	4.4587	0.0347	0.824	0.688	0.986
Donor Gender (0=F 1=M 0.5=Mixed	1	-0.53320	0.17707	9.0680	0.0026	0.587	0.415	0.830
Total IEQs (all infusions)	1	0.19479	0.09227	4.4567	0.0348	1.215	1.014	1.456
IMPDH-Inh + Calcin-Inh	1	1.53747	0.51048	9.0709	0.0026	4.653	1.711	12.654

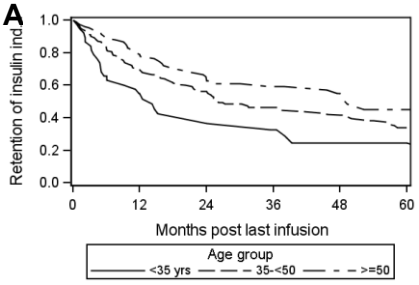
H



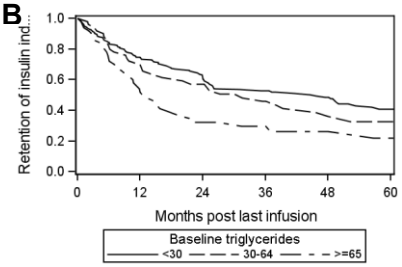
Many factors influence retention of insulin independence post last infusion. The factors that remain in a multivariable model include recipient age>35 years (Exhibit 5-3A, p=0.01), baseline triglycerides<65mg/dL (B, p=0.001), donor treated with insulin (C, p=0.02), donor in-hospital transfusion (D, p=<0.001) and vasopressor (E, p=0.003), and induction with T-cell depleting agents and TNF-a inhibitors (D, p=0.04). Note that the event being modeled is loss of insulin independence with lower hazard favorable, though the retention (survival) of insulin independence is plotted.

Exhibit 5-3
Retention of Insulin Independence Post Last Infusion
(Censored at final graft loss or end of follow-up)

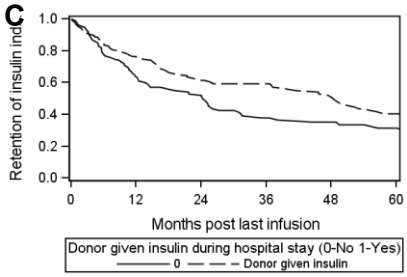
A



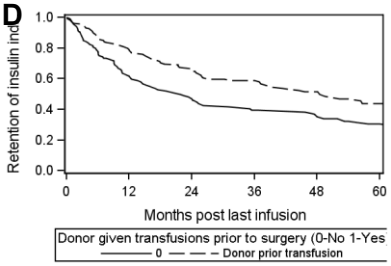
B



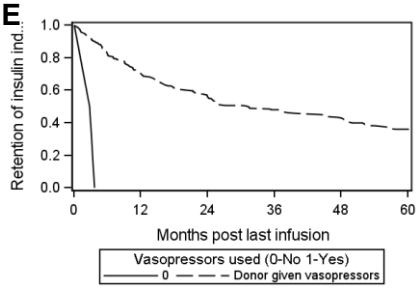
C



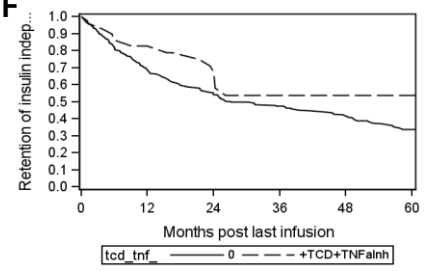
D



E

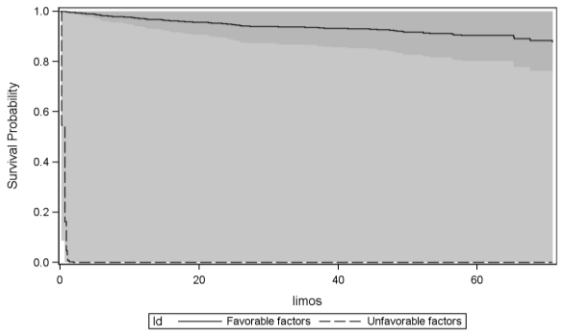


F



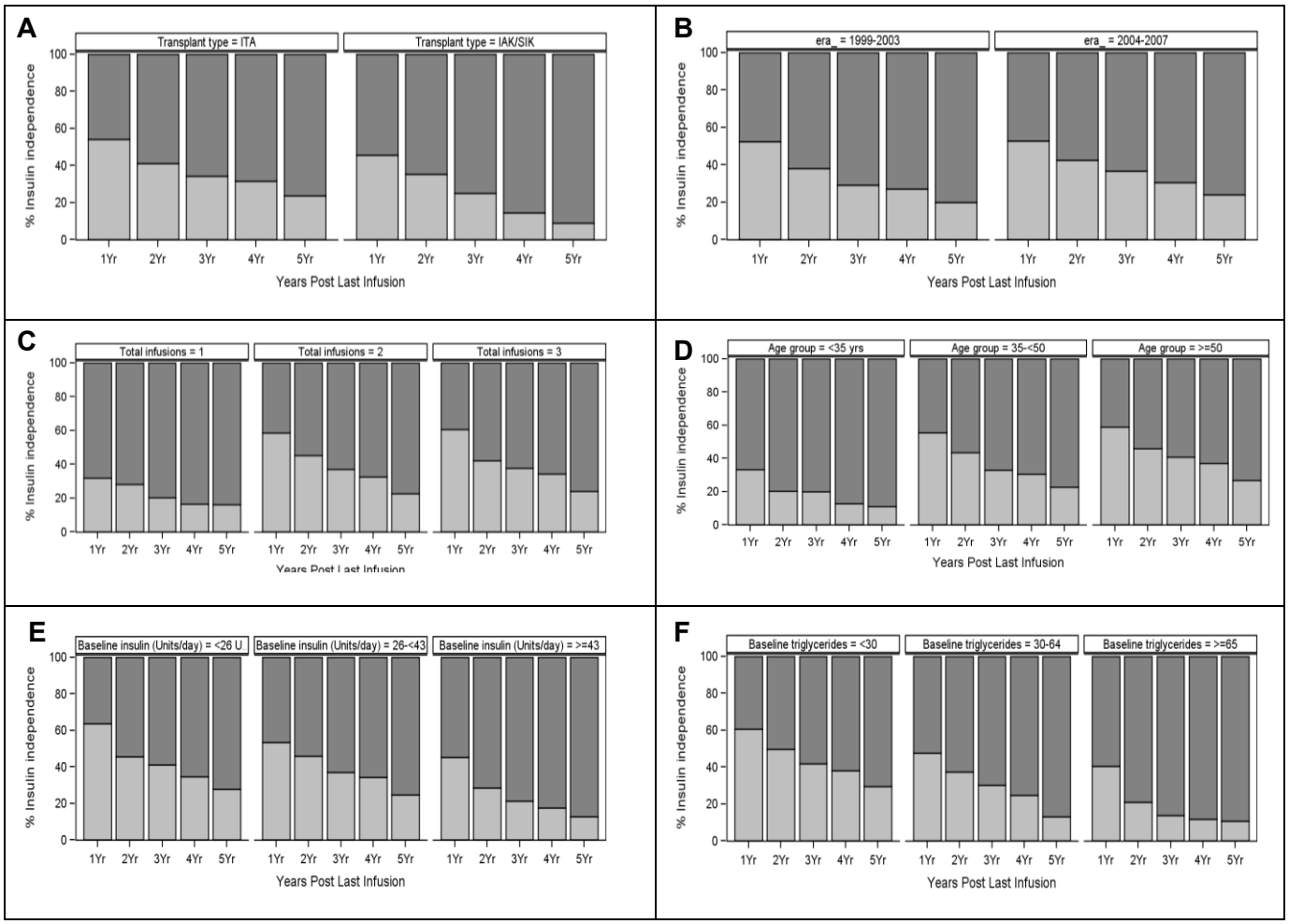
G. Final multivariate model	DF	Parameter	Standard	Chi-	Pr > ChiSq	Hazard	95% Hazard Ratio	
Recipient age group	1	-0.36474	0.14372	6.4406	0.0112	0.694	0.524	0.920
Baseline microinsulin (+)	1	-1.15430	0.65434	3.1119	0.0777	0.315	0.087	1.137
Baseline triglycerides	1	0.34820	0.10778	10.4372	0.0012	1.417	1.147	1.750
Donor given transfusions prior	1	-0.71721	0.18137	15.6378	<.0001	0.488	0.342	0.696
Donor given insulin during	1	-0.41351	0.18070	5.2369	0.0221	0.661	0.464	0.942
Vasopressors used (0-No 1-Yes)	1	-3.58546	1.19888	8.9441	0.0028	0.028	0.003	0.291
T-Cell depletion (0-No 1-Yes)	1	-0.65511	0.31651	4.2839	0.0385	0.519	0.279	0.966

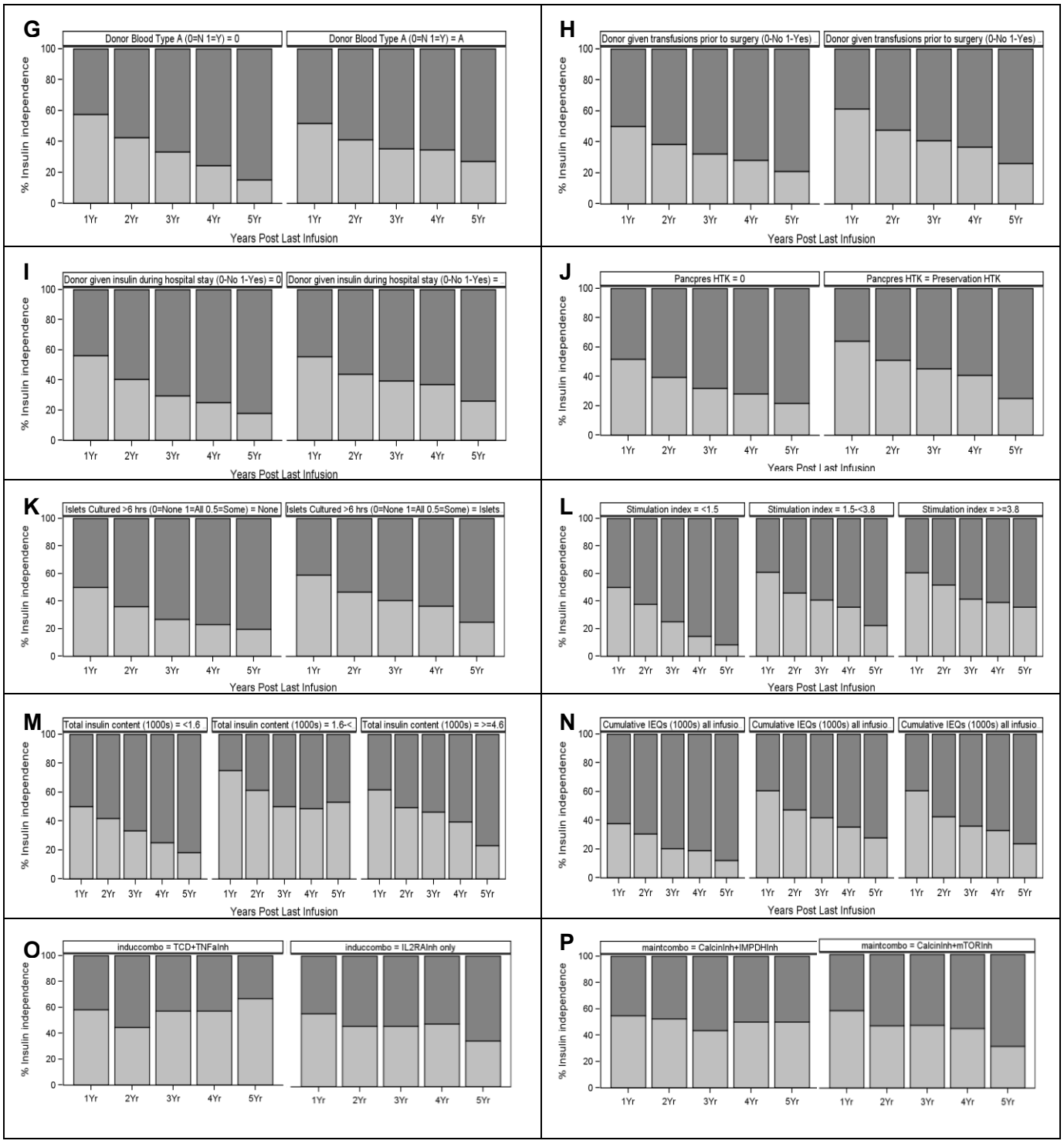
H



Prevalence of insulin independence post last infusion is the optimal way to characterize the probability of being insulin independent in follow-up time post islet transplantation, because insulin independence can be lost and re-gained, often over periods spanning months or years. Prevalence also reconciles disparities in factors that may be predictive of retention but not of achievement, or vice versa (Exhibits 5-2 and 5-3). However, multivariate analysis of prevalence is much more complex because of non-linearity over the multiple time points and the high order of interactions that are required by the model to test for changes in the response across 2-3 levels each of several predictors (e.g., type of transplant, baseline characteristics, etc.) over time. Nonetheless, prevalence rates of insulin independence post last infusion, shown for factors univariately predictive of the outcome (Exhibit 5-4), are: ITA vs. IAK/SIK (A, p=0.01), which is likely explained by other variables and is the topic of a focus analysis); era (B, p=0.01); two but not ≥3 infusions (C, p<0.001); recipient age >35 years (D, p<0.001); baseline insulin <0.43U/kg/day (E, p=0.004); baseline triglycerides <30 mg/dL (F, p=0.001), ABO type A (G, <0.001), donor transfused prior to recovery (H, p=0.04). donor given insulin (I, p=0.01), HTK preservation (J, p=0.04), islets cultured>6 hrs (K, p=0.02), islet stimulation index>1.5 (L, p=0.05), islets total insulin ≥1.6 (M, p=0.01), total IEQs over all infusions>600K (N, p=0.01), induction with TCD+TNFa-inhibition (O, p=0.005), and maintenance with CNI+IMPDH-inhibitor (P, p=0.02).

Exhibit 5-4
Prevalence of Insulin Independence Post Last Infusion

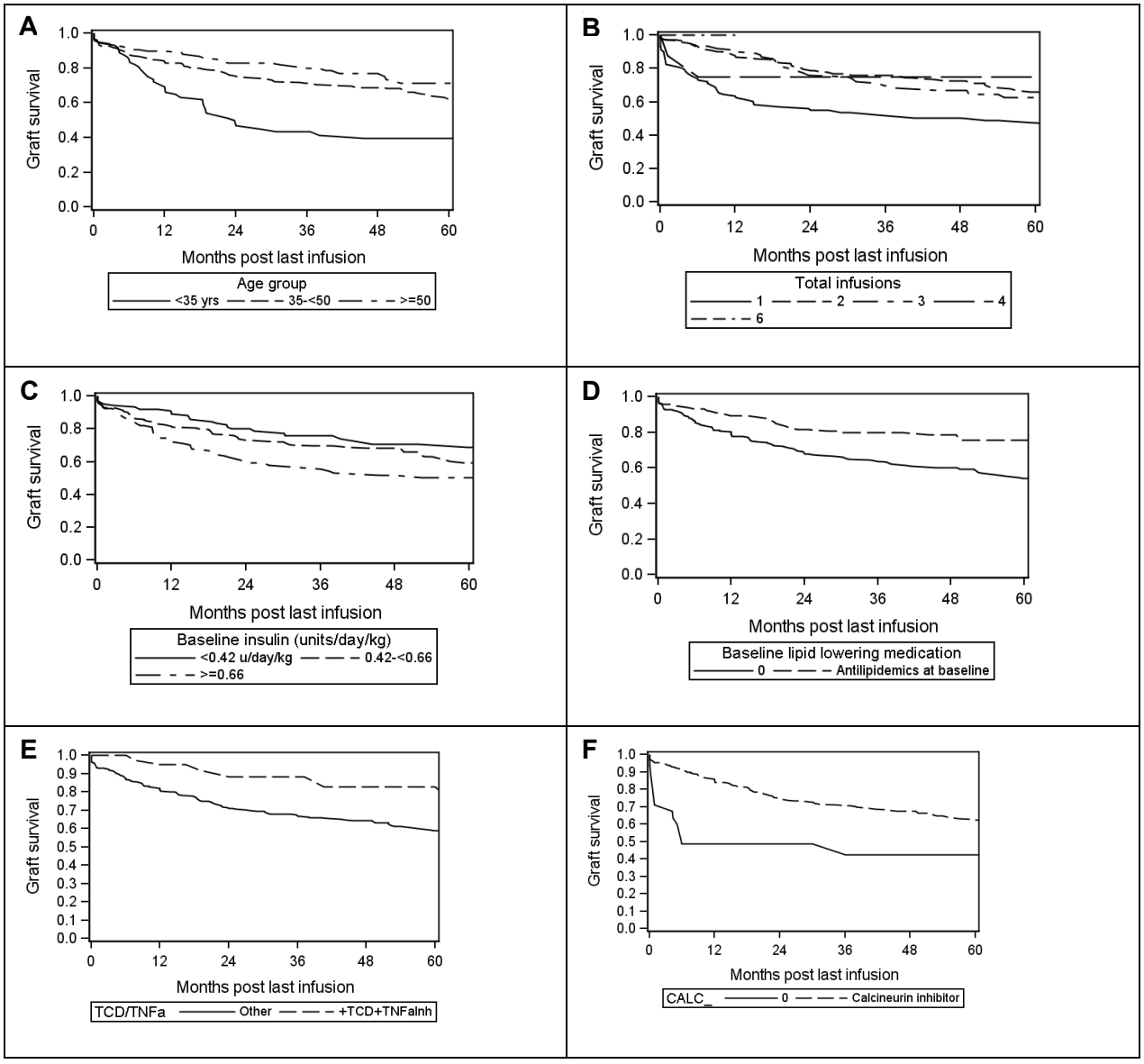



G
Donor Blood Type A (0=N 1=Y) = 0
Donor Blood Type A (0=N 1=Y) = A
H
Donor given transfusions prior to surgery (0-No 1-Yes) ..
Donor given transfusions prior to surgery (0-No 1-Yes) ..
I
Donor given insulin during hospital stay (0-No 1-Yes) = 0
Donor given insulin during hospital stay (0-No 1-Yes) =
J
Pancpres HTK = 0
Pancpres HTK = Preservation HTK
K
Islets Cultured >6 hrs (0=None 1=All 0.5=Some) = None
Islets Cultured >6 hrs (0=None 1=All 0.5=Some) = Islets
L
Stimulation index = <1.5
Stimulation index = 1.5-<3.8
Stimulation index = >=3.8
M
Total insulin content (1000s) = <1.6
Total insulin content (1000s) = 1.6-<
Total insulin content (1000s) = >=4.6
N
Cumulative IEQs (1000s) all infusio..
Cumulative IEQs (1000s) all infusio..
Cumulative IEQs (1000s) all infusio..
O
induccombo = TCD+TNFaInh
induccombo = IL2RAInh only
P
maintcombo = CalcinInh+IMPDHInh
maintcombo = CalcinInh+mTORInh
% Insulin independence
0
20
40
60
80
100
1Yr
2Yr
3Yr
4Yr
5Yr
Years Post Last Infusion

C-peptide≥0.3 ng/mL.

Of all 1,072 allogeneic islet infusions, 25 (2.3%) resulted in primary non-function (C-peptide never ≥0.3 ng/mL up to reinfusion): 3.5% in 1999-2003, 1.3% in 2004-2006, and 2.1% in 2007-2009. By recipient, retention of graft function (C-peptide≥0.3 ng/mL) post last infusion is maximized by recipient age>35 years (exhibit 5-5A, p<0.001), >1 infusion (B, p=0.002), baseline insulin <0.66 U/day/kg, T-cell depletion plus TNF-a inhibition (E, p=0.02), and use of calcineurin inhibitors (F, p=0.02). The final multivariate model is shown in Exhibit 5-5G, with the best-worst combinations of factors in panel H.

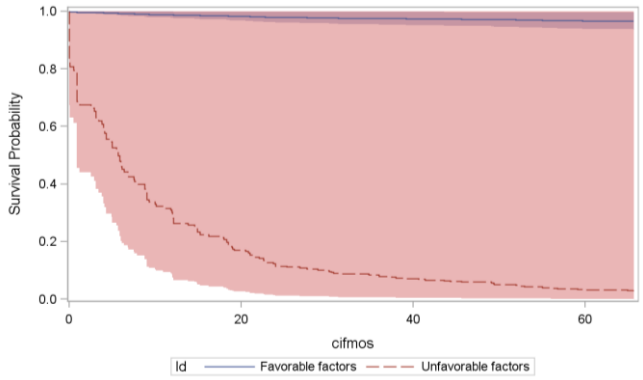
Exhibit 5-5
Retention of C-peptide ≥0.3 ng/mL Post Last Infusion
(Censored at end of follow-up)



G

Final multivariate mo el	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Total infusions	1	-0.39191	0.12567	9.7252	0.0018	0.676	0.528	0.865
Age group	1	-0.48215	0.14105	11.6844	0.0006	0.617	0.468	0.814
List days	1	-0.36628	0.13325	7.5558	0.0060	0.693	0.534	0.900
Baseline insulin (units/day/kg)	1	0.29158	0.13236	4.8531	0.0276	1.339	1.033	1.735
Baseline lipid lowering medication	1	-0.54472	0.21837	6.2227	0.0126	0.580	0.378	0.890
TCD+CalcinInh	1	-1.58967	0.67316	5.5767	0.0182	0.204	0.055	0.763

H



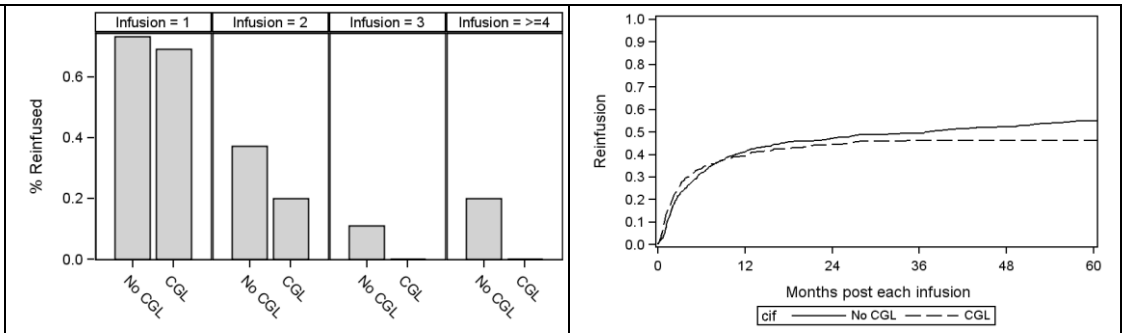
Re-infusion

Re-infusion may have been conducted without (366/727=50%) or after (139/432=32%) complete graft failure (fasting C-peptide<0.3 ng/mL without recovery, Exhibit 5-6A). A number of re-infusions were conducted while the patient was not only C-peptide positive but also insulin independent (Exhibit 5-6B; 53/229=23%, for all infusions). Re-infusion was much more likely when the patient was not insulin independent (p<0.001).

Exhibit 5-6
Re-Infusion
(All infusions)

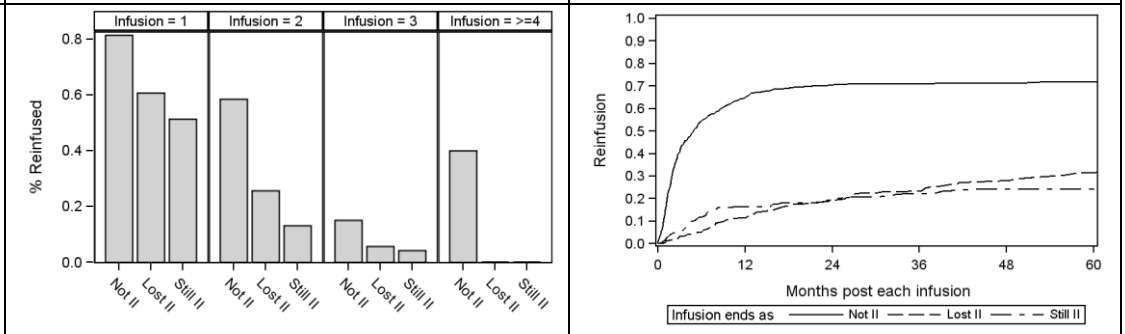
A

By C-peptide ≥0.3 ng/mL



B

By insulin indepen-dence



Factors associated with improved outcomes in fasting blood glucose, HbA1c, and severe hypoglycemia are fully exhibited in on-line Supplement A-4S. Comparisons by era and type of transplant are shown in Exhibits 5-7 to 5-9). HbA1c levels improved somewhat in 2004-2007 (p=0.06).

Exhibit 5-7
Fasting blood glucose 60-150 mg/mL post last infusion

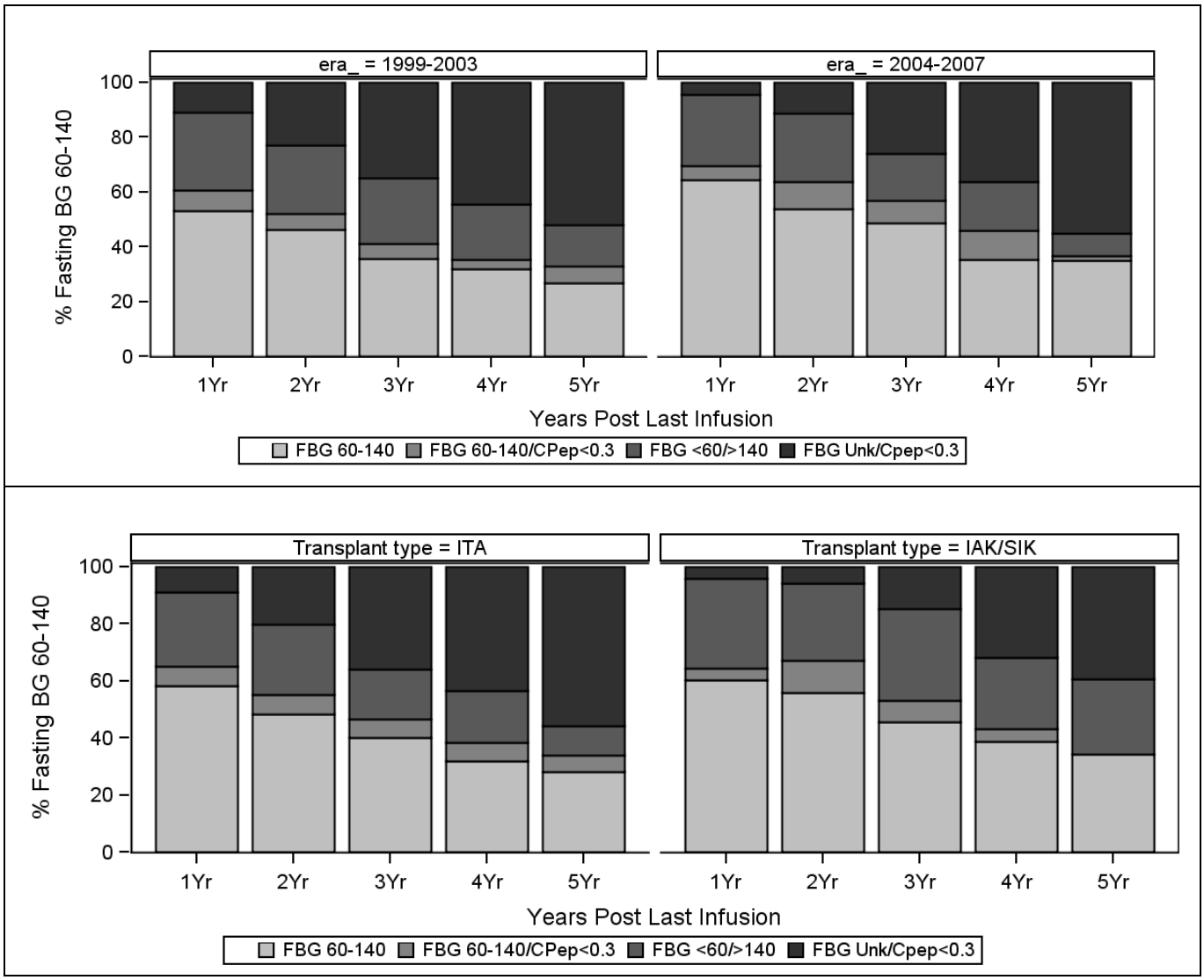


Exhibit 5-8
HbA1c<6.5% or drop by 2% post last infusion

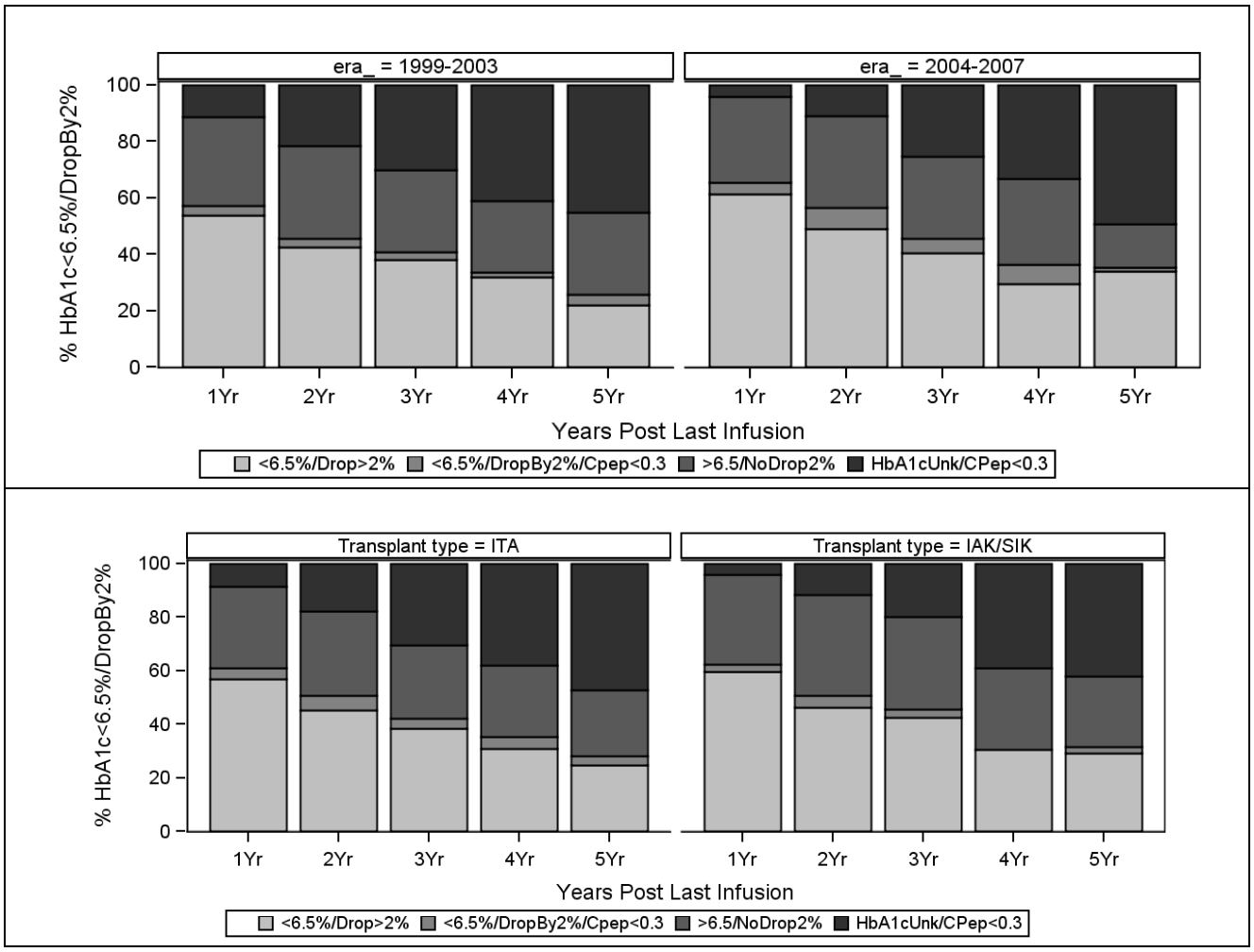
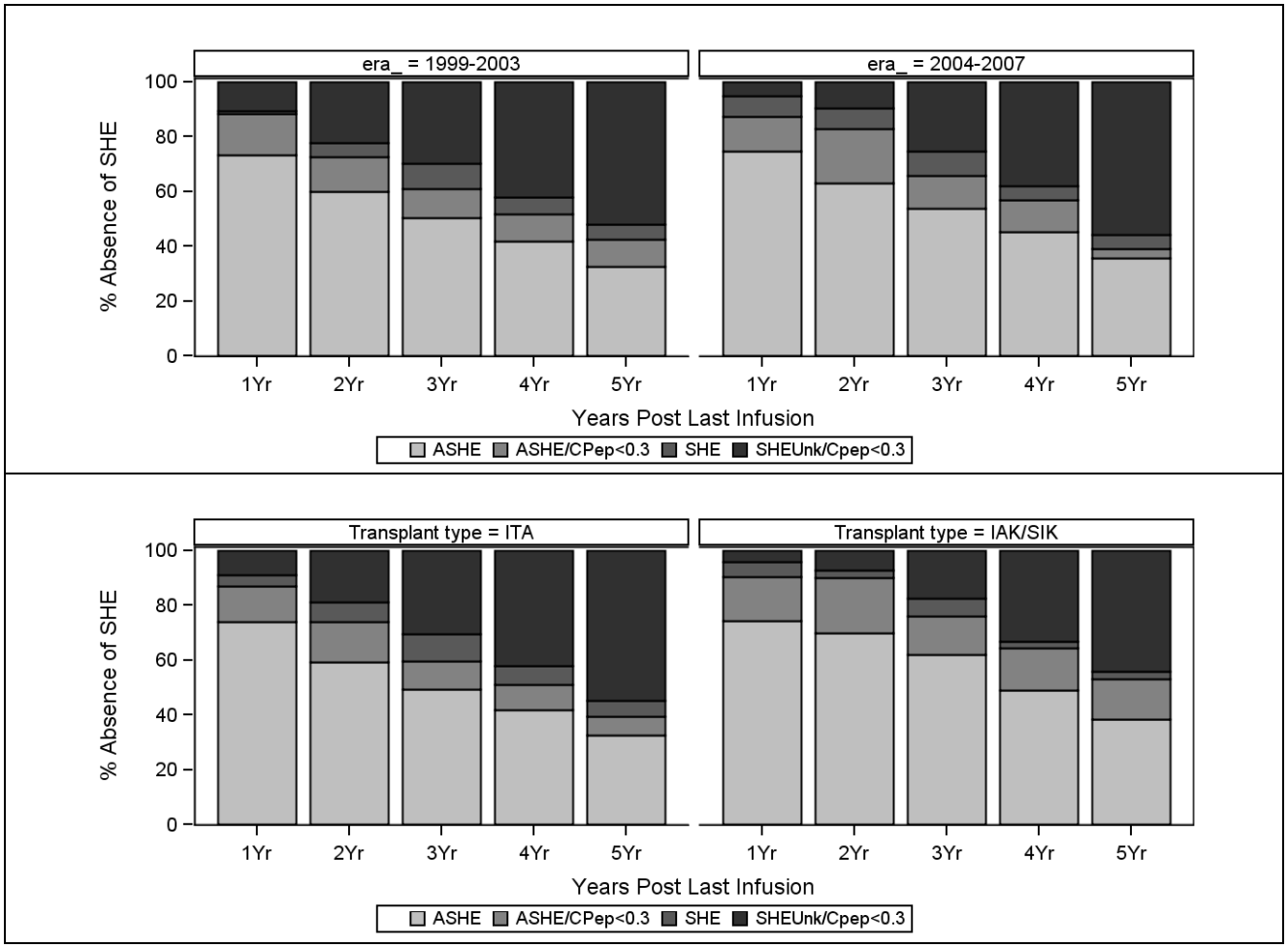


Exhibit 5-9
Absence of severe hypoglycemia post last infusion



Levels of daily insulin requirement (U/day) declined dramatically after islet transplantation (Exhibit 5-10, p<0.001), with some return upwards over 5 years of follow-up (this analysis includes 0 U/day for periods of insulin independence). Fasting C-peptide rises dramatically after islet transplantation, with decline over 5 years although more than 50% retain C-peptide>0.3 ng/mL at 5-years post last infusion (Exhibit 5-11). The improvement in 2004-2007 is significant (p<0.01). HbA1c declines sharply after islet transplantation, and does not return to pre-transplant levels (p<0.01, Exhibit 5-12). Fasting blood glucose also declines dramatically and remains at levels of 80-120 mg/dL (p<0.01, Exhibit 5-13).

Exhibit 5-10
Insulin dose (U/day) post last infusion

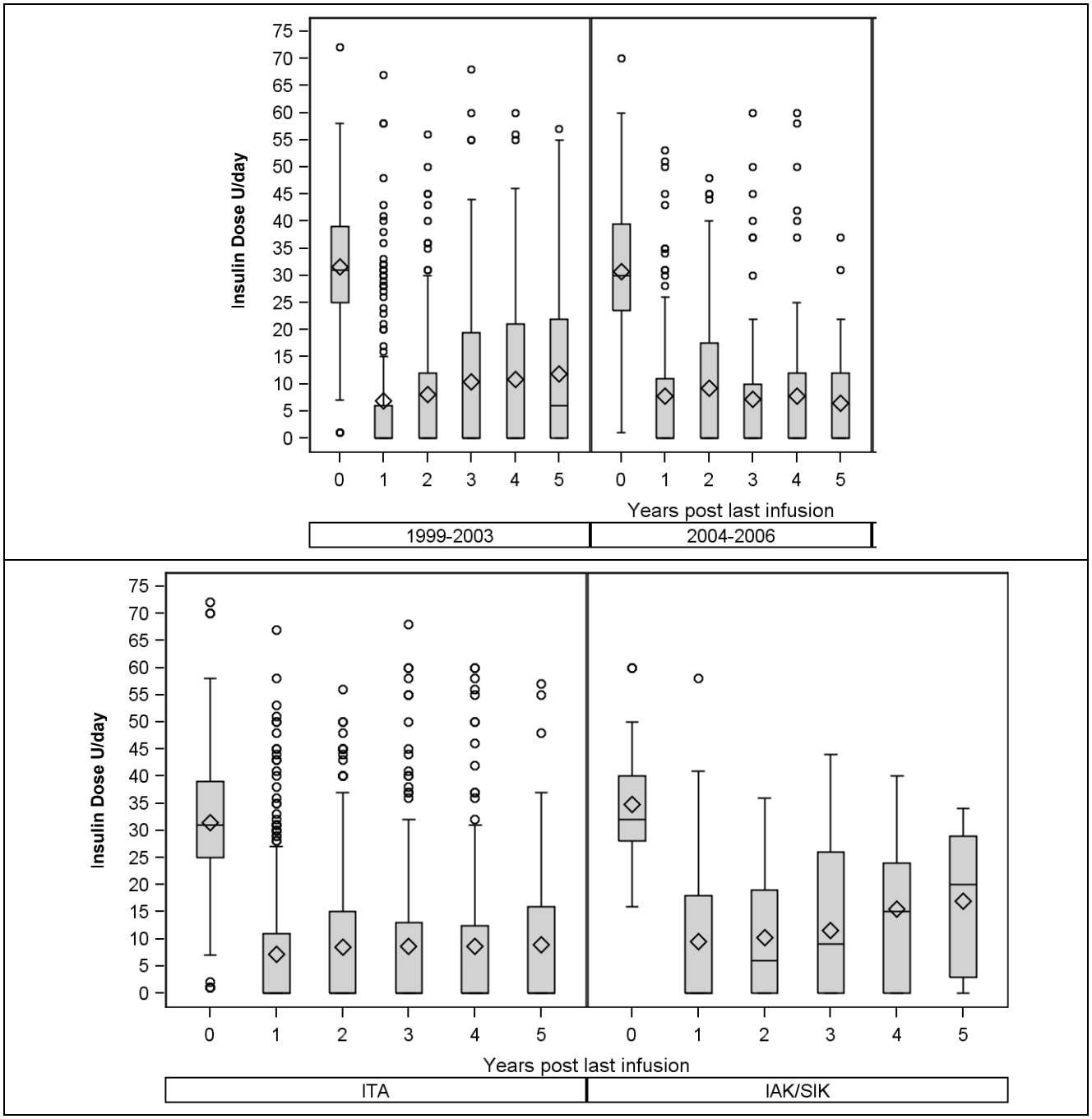


Exhibit 5-11
Fasting C-peptide (ng/ml) post last infusion

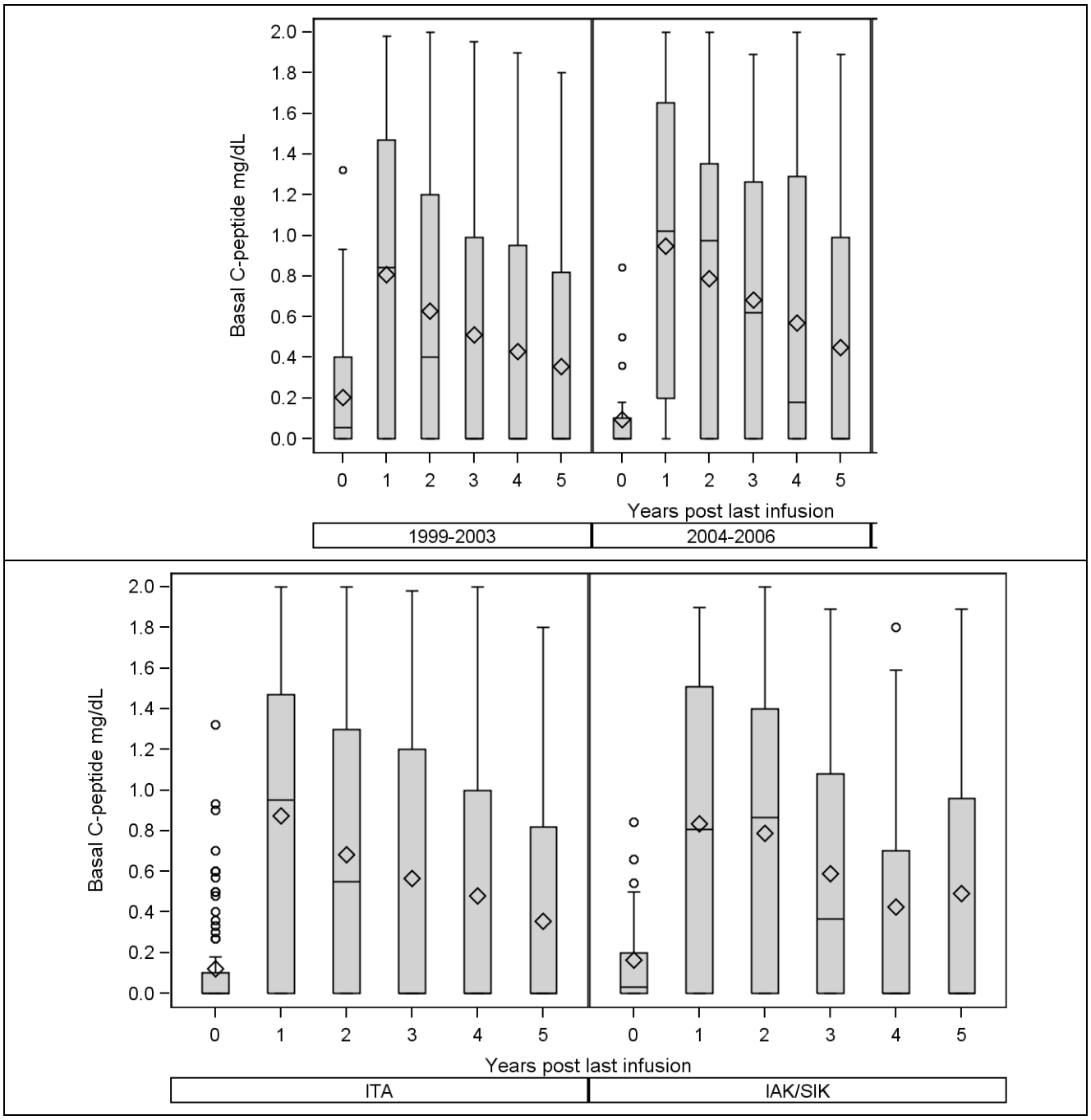


Exhibit 5-12
HbA1c (%) post last infusion

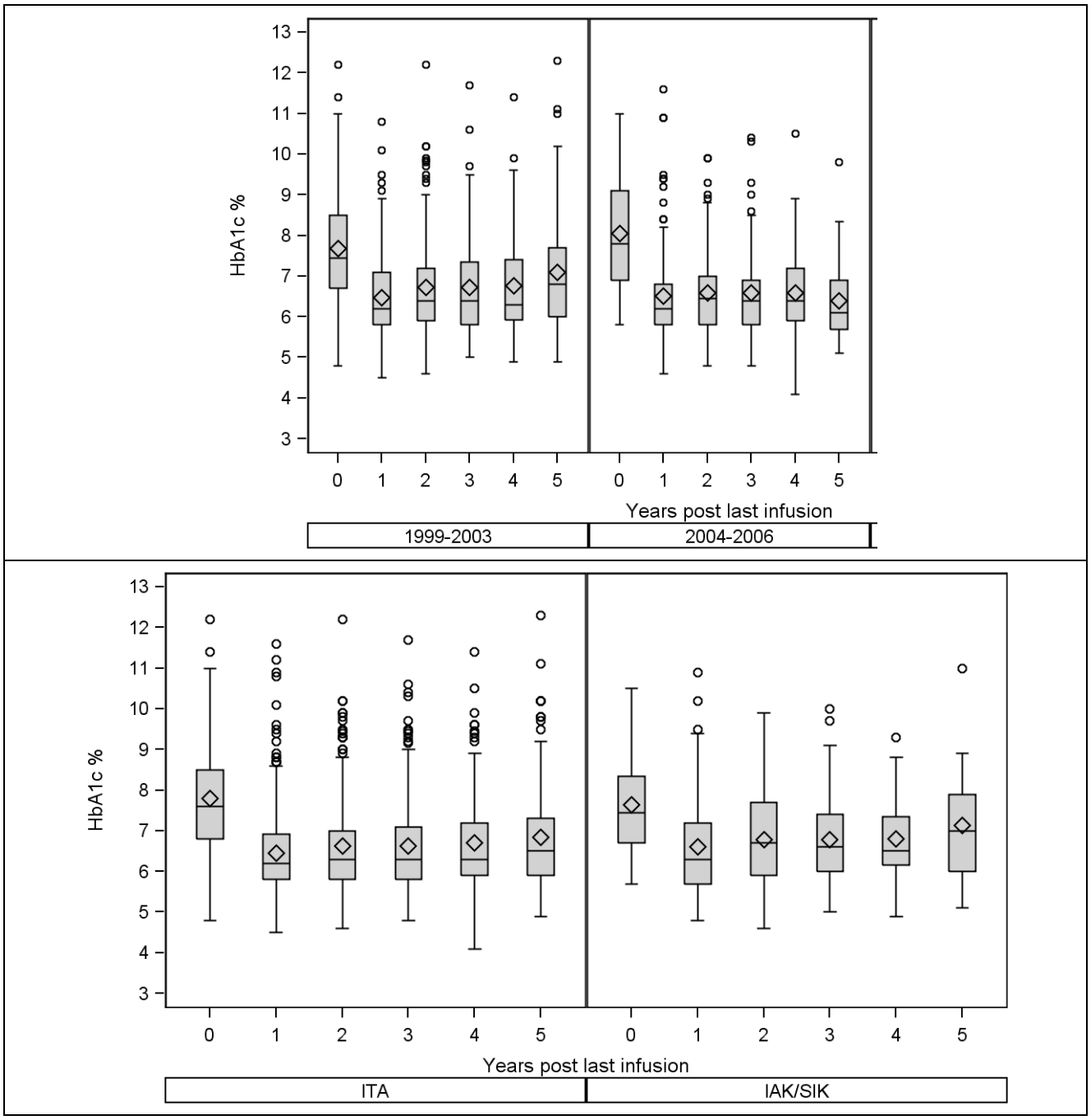
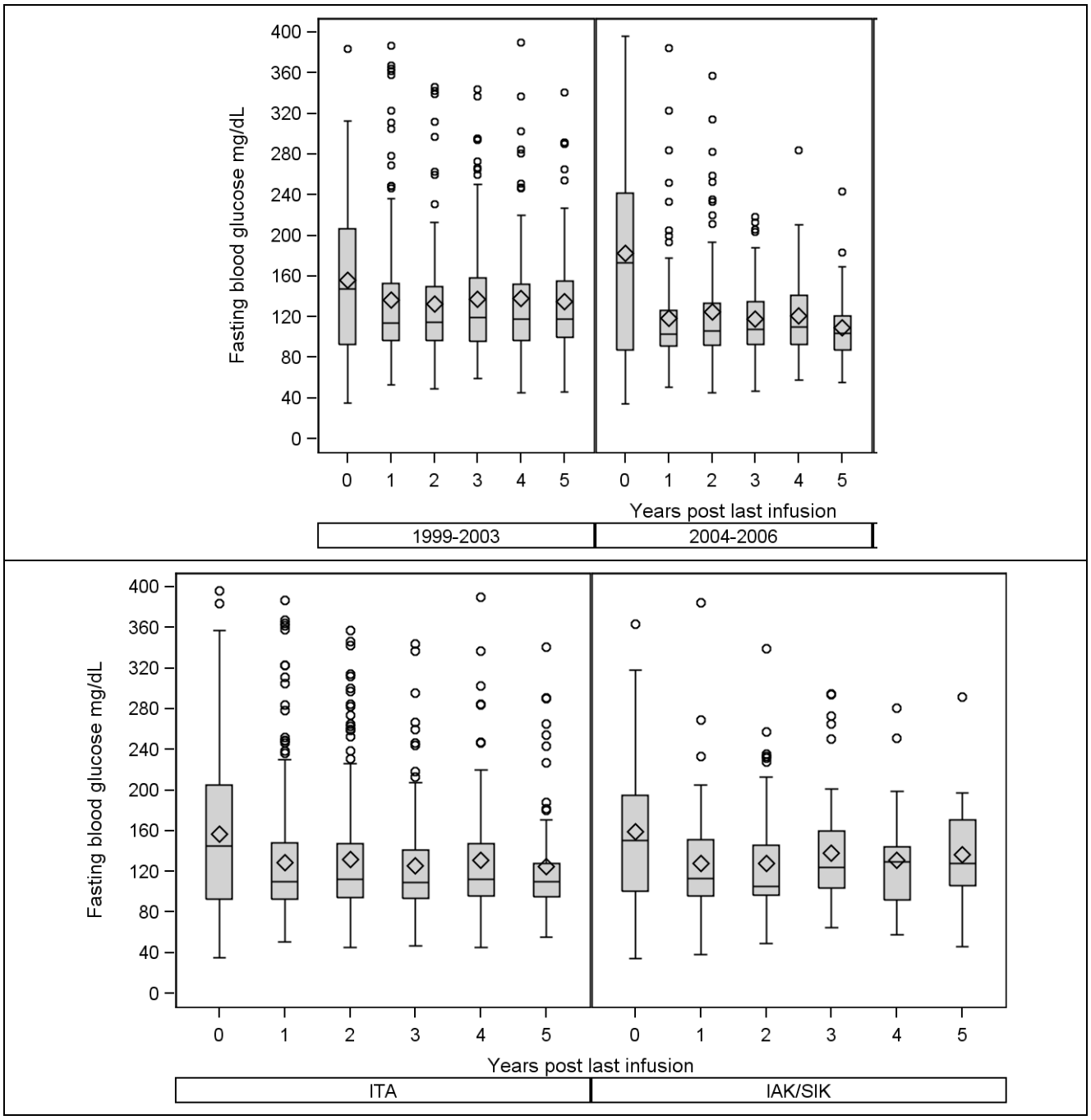


Exhibit 5-13
Fasting blood glucose (mg/dl) post last infusion

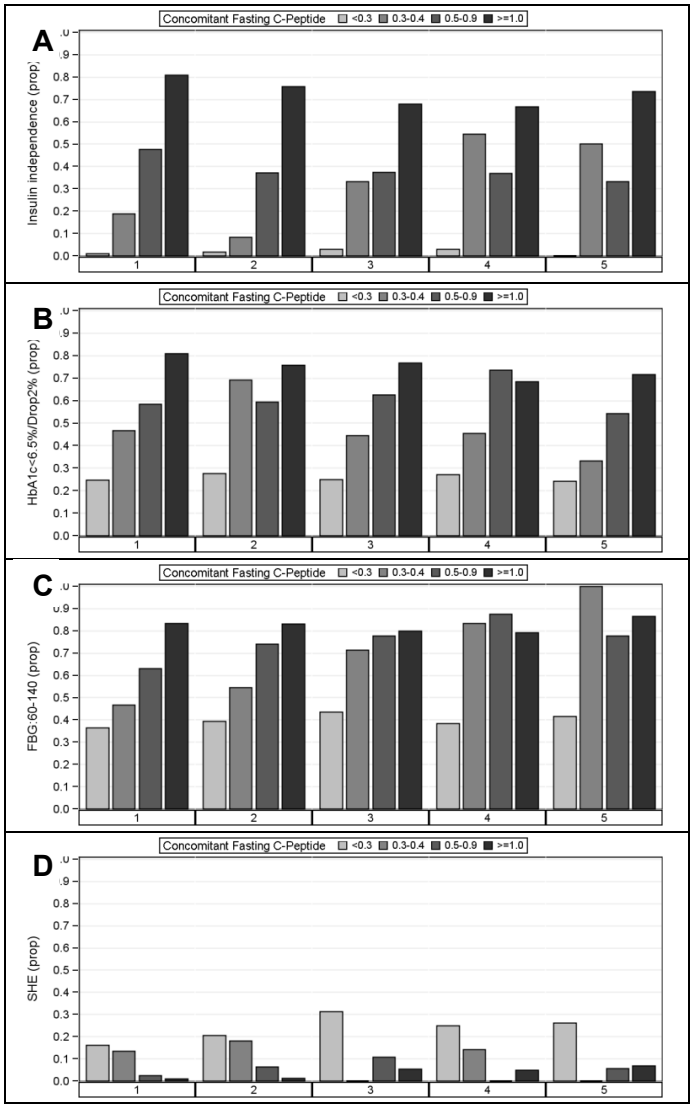


The higher the fasting C-peptide level, the higher the likelihood of insulin independence, HbA1c<6.5% or drop by 2%, FBG of 60-140, and the lower the likelihood of severe hypoglycemia (Exhibit 5-14). Even partial graft function, i.e., fasting C-peptide of 0.3-0.5 ng/mL, is associated with lowered insulin use, improved HbA1c, greater glycemic control, and lower levels of severe hypoglycemia, which occurs less than 30% at any follow-up, a substantial reduction from the baseline level of about 70%. While these strong associations among the co-primary outcomes are highly significant, any causal relationships cannot be deduced just from the associations; rather, they require a more detailed analysis of the temporal relationships.

Exhibit 5-14

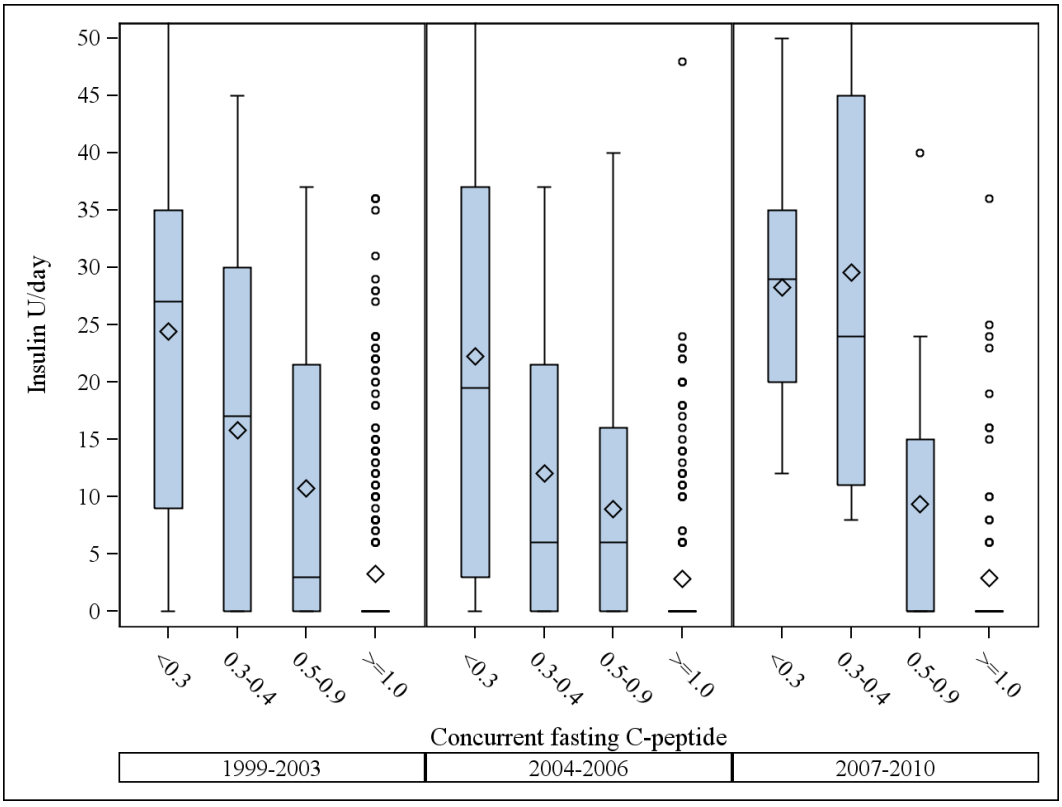
Association of C-peptide level (ng/mL) with other primary outcomes

At years 1-5 post last infusion



Exogenous insulin requirement (U/day) declines rapidly after islet transplantation (Exhibit 5-14): the higher the concurrent C-peptide level, the lower the insulin requirement (p<0.001).

Exhibit 5-15
Insulin use (U/day) according to concurrent C-peptide level
Years 1-5 post last infusion (pooled)



Ns	1999-2003 Insulin U/day			2004-2006 Insulin U/day			2007-2010 Insulin U/day		
	N	Mean	Std	N	Mean	Std	N	Mean	Std
Concurrent fasting C-peptide									
<0.3 ng/mL	117	24.5	18.0	76	22.3	18.3	26	28.3	10.6
0.3-0.4	22	15.8	16.3	12	12.0	14.1	9	29.6	19.6
0.5-0.9	84	10.7	14.3	46	8.9	11.2	13	9.4	12.7
>=1.0	325	3.3	7.5	211	2.8	6.7	78	2.9	7.1

SUMMARY

Taken from the combined evidence in these analyses, the following observations emerge regarding factors influencing good clinical outcomes of islet transplantation:

- Retention of insulin independence and graft function improved from 1999-03 to 2004-06, with the improvements accounted for by differences in identifiable factors such as older recipient age, lower insulin requirement, and shifts in immunosuppressive strategies;
- Two (but not three or more) infusions and higher total IEQs infused resulted in improved outcomes, although the decision to re-infuse is based at least in part on previous success (at least not permanent graft loss) and many other non-biological factors
- LDL cholesterol
- Donor management with vasopressors, transfusion and insulin result in improved clinical outcomes
- Donor age <35 seems a favorable factor
- The use of thermolysin, as an added preservation technique, improves clinical outcomes
- Culturing the islets >6 hours improves clinical outcomes
- An induction combination that includes T-cell depletion and TNF-antagonism improves clinical outcomes to 50% insulin independence at 5-years
- A maintenance combination that includes calcineurin inhibition and IMPDH inhibition similarly results in higher long-term benefit.

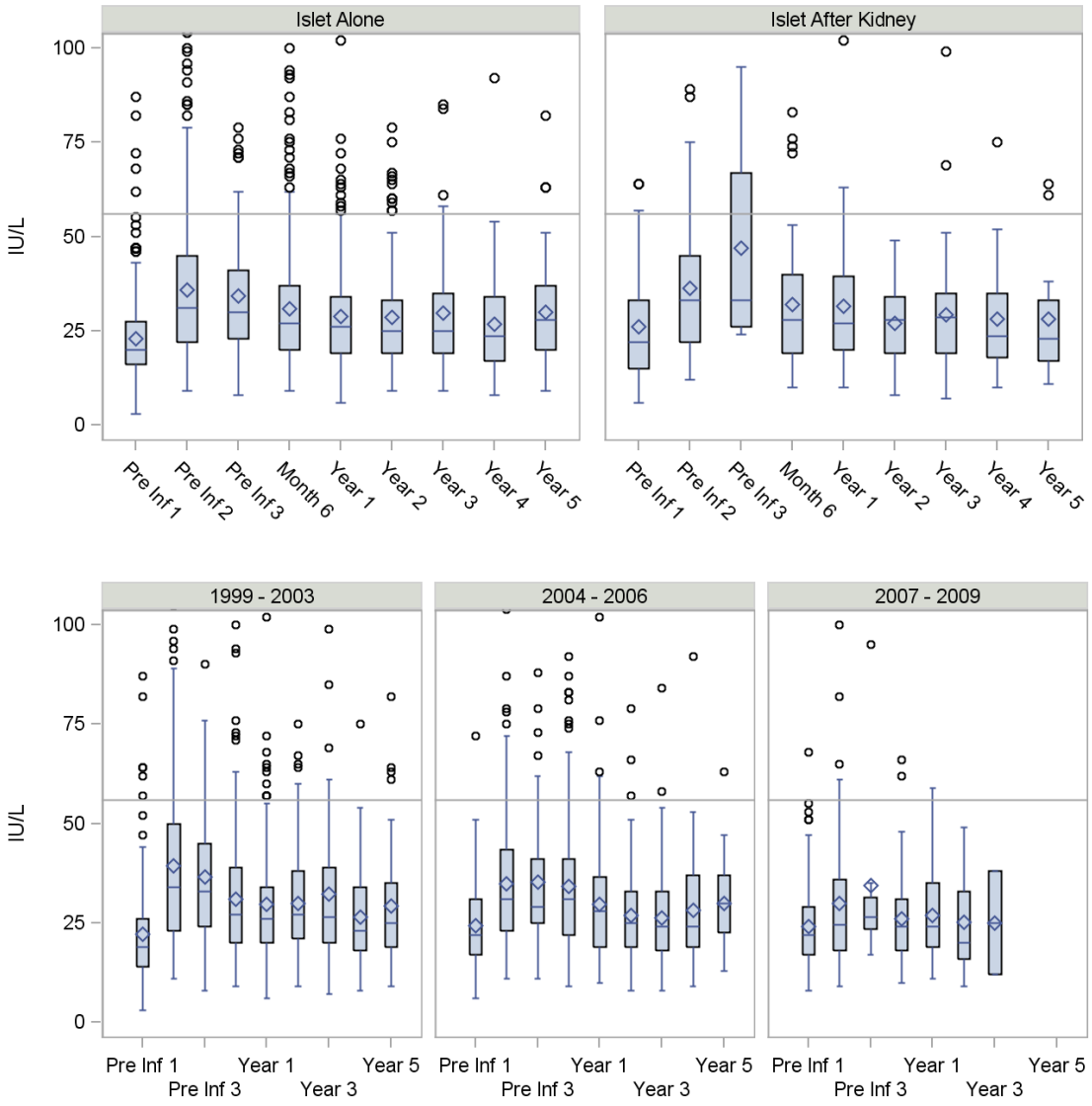
Chapter 6
Liver, Kidney, Lipid and PRA Effects

Introduction

Exhibit 6-1 to 6-15 display various laboratory results at major time points following islet transplantation according to type of transplant and era. In the early era 1999-2003, ALT (Exhibit 6-1) and AST (Exhibit 6-2) rose immediately post infusion and then returned to pre-transplant levels; this rise was not seen in the most recent era. A similar pattern is seen for LDL cholesterol (Exhibit 6-7). Triglycerides (Exhibit 6-8) rose very slowly over follow-up post transplantation, and more so in the most recent era; natural history information is required for comparison. Serum creatinine (Exhibit 6-9) rose steadily post transplantation but less so in 2004-2006 and perhaps 2007-2009; here also, comparisons to non-diabetics and to T1D absent islet transplantation would be useful. Serum creatinine rose by 30% (Exhibit 6-10) most frequently in the early era, which has not been seen in the most recent era. Estimated GFR (Exhibit 6-13) declined in both ITA and IAK/SIK groups, more markedly in the early era and less so in the more recent era. Class 1 PRA (Exhibit 6-14) increases post islet transplantation (in the early time points post infusion, the boxes are collapsed to zero, and they expand upward slightly at 2-5 years).

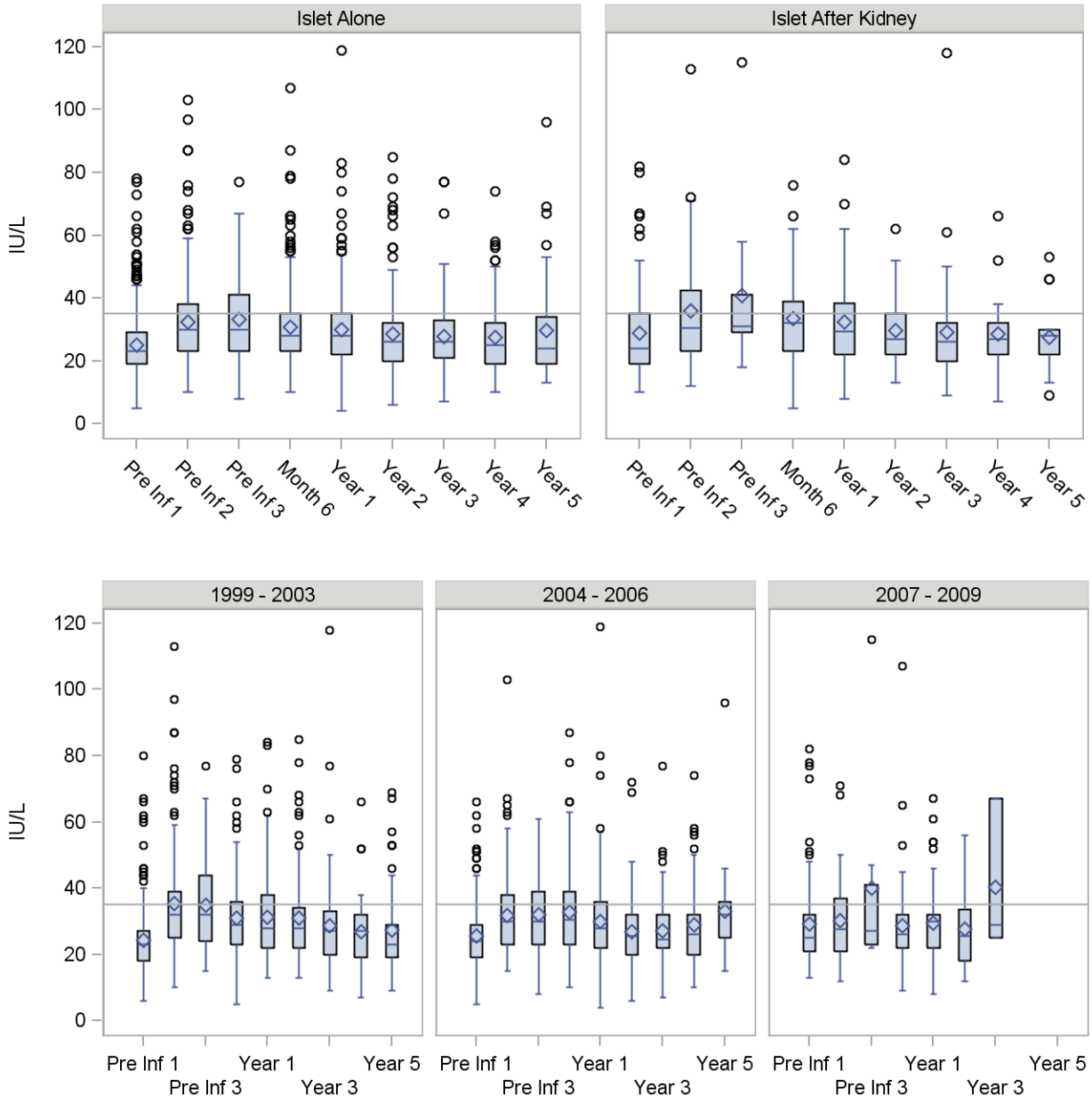
Exhibits 6-16 to 6-28 show the same laboratory results according to induction and maintenance immunosuppression at each time post infusion. There are no remarkable deviations from the observations made above that are attributable to any particular immunosuppression regimen according to these broad categories.

Exhibit 6-1
ALT(IU/L) by Infusion Type and Era



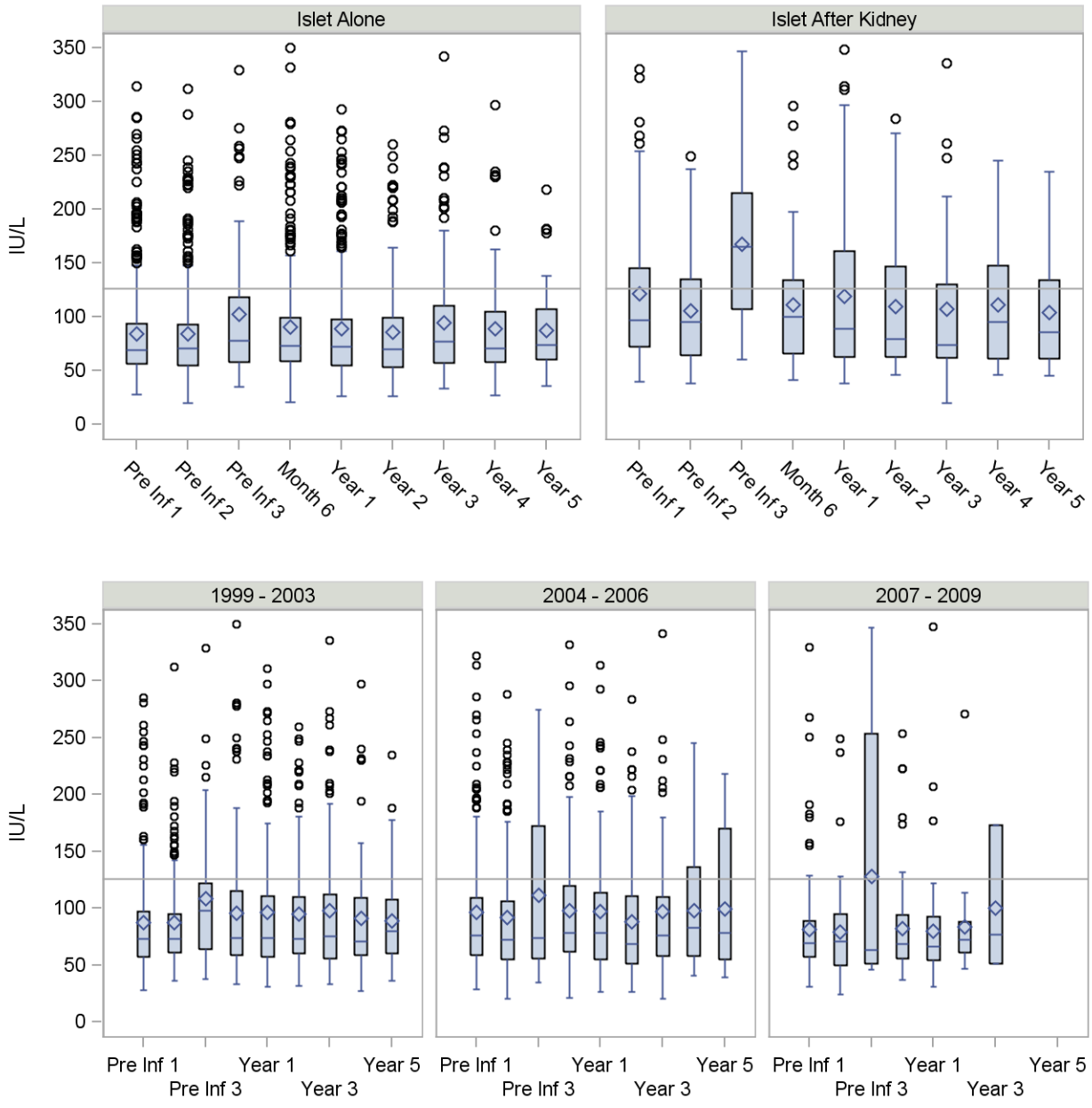
	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	389	263	82	262	253	155	115	89	49
Islet After Kidney	73	60	14	58	60	46	40	24	17
1999 - 2003	199	142	53	141	140	96	84	69	46
2004 - 2006	167	123	35	114	121	84	68	44	20
2007 - 2009	96	58	8	65	52	21	3	.	.

Exhibit 6-2
AST(IU/L) by Infusion Type and Era



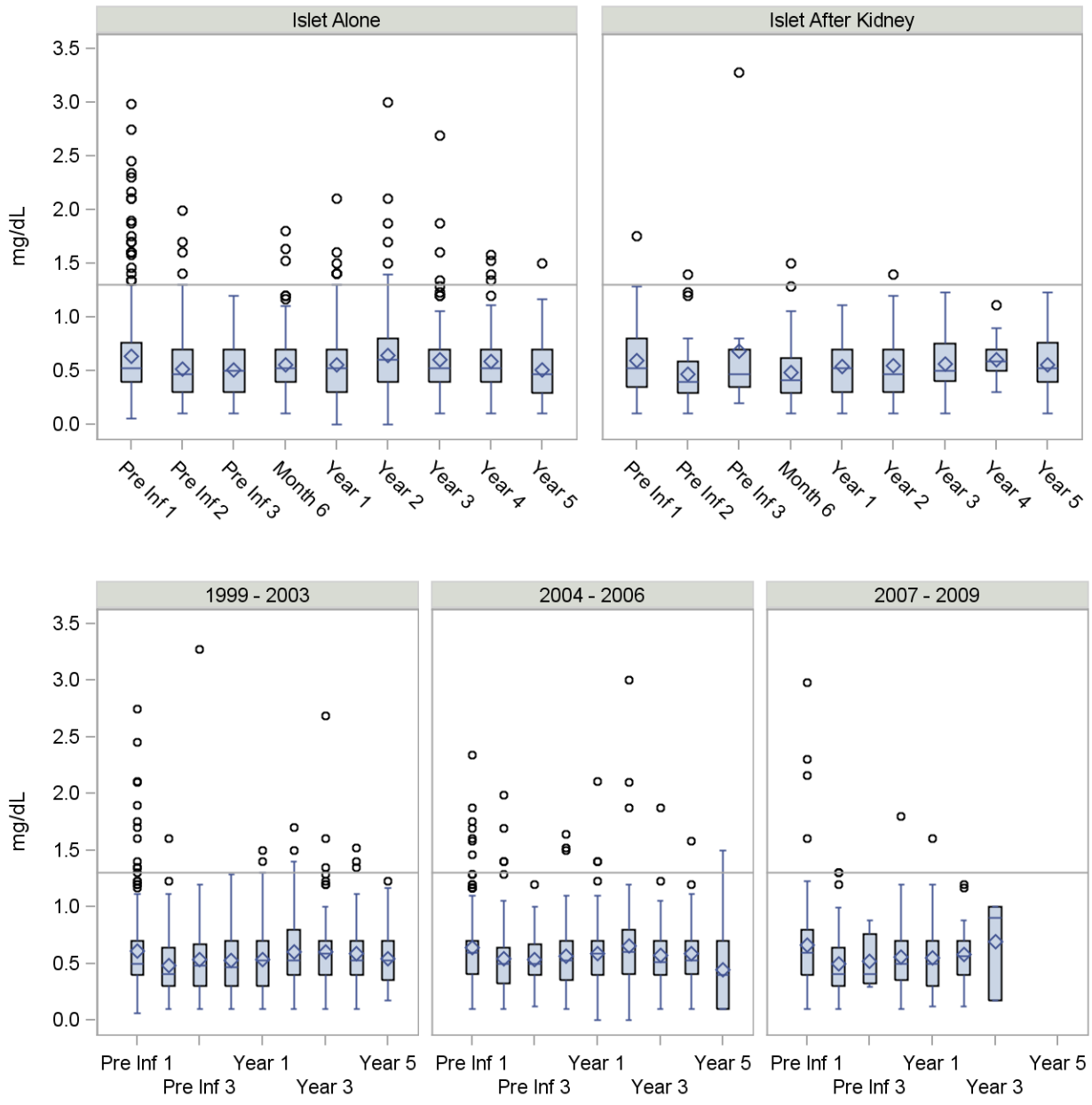
	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	397	283	90	295	279	165	127	94	54
Islet After Kidney	74	60	13	58	60	46	40	23	17
1999 - 2003	207	152	57	154	150	100	94	75	50
2004 - 2006	173	135	38	133	137	91	70	42	21
2007 - 2009	91	56	8	66	52	20	3	.	.

Exhibit 6-3
Alkaline Phosphatase(IU/L) by Infusion Type and Era



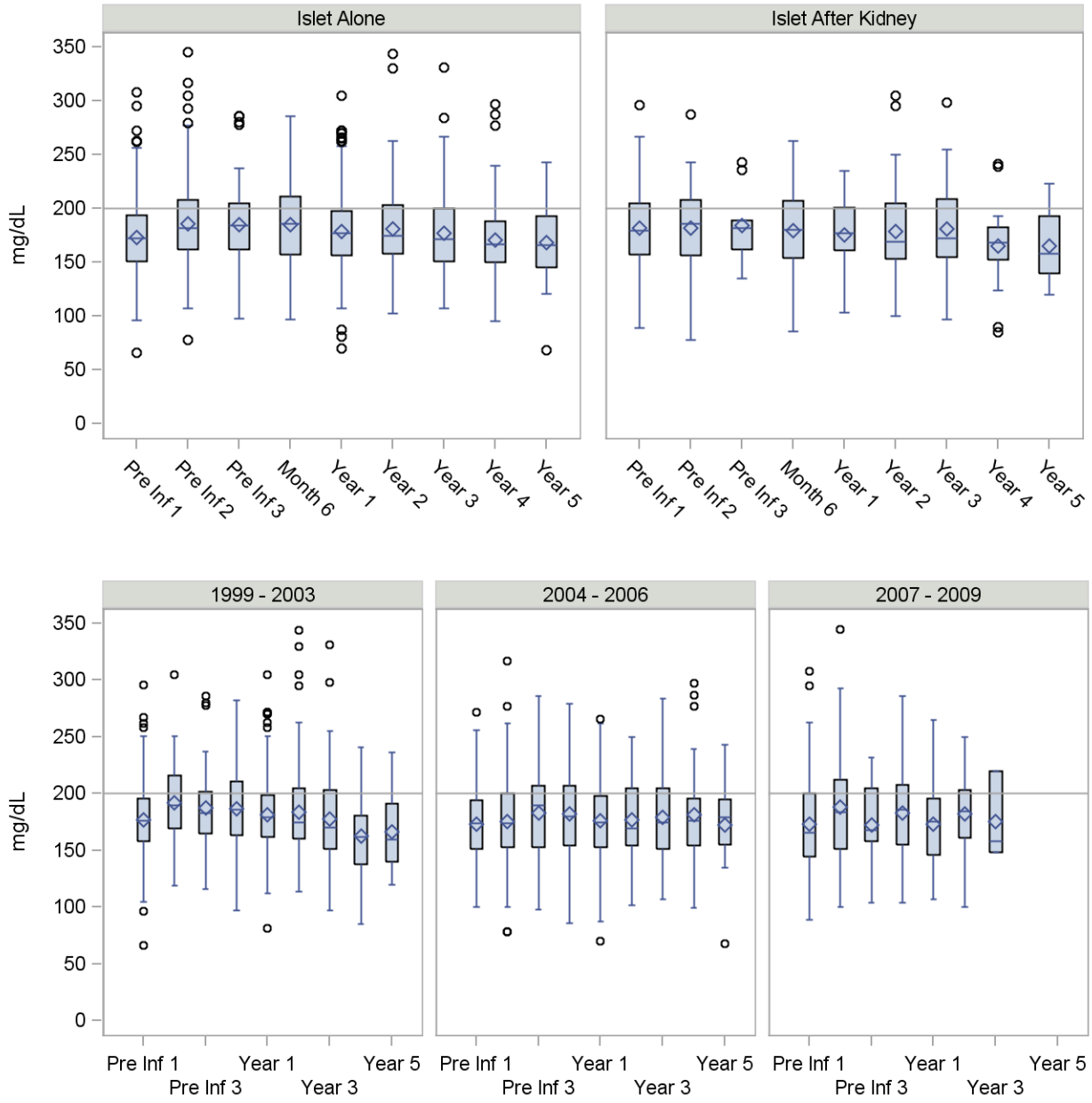
	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	397	279	85	278	277	161	124	89	50
Islet After Kidney	73	60	13	56	60	45	38	24	17
1999 - 2003	200	146	53	143	151	101	93	74	48
2004 - 2006	169	135	38	127	134	86	66	39	19
2007 - 2009	101	58	7	64	52	19	3	.	.

Exhibit 6-4
Total bilirubin(mg/dL) by Infusion Type and Era



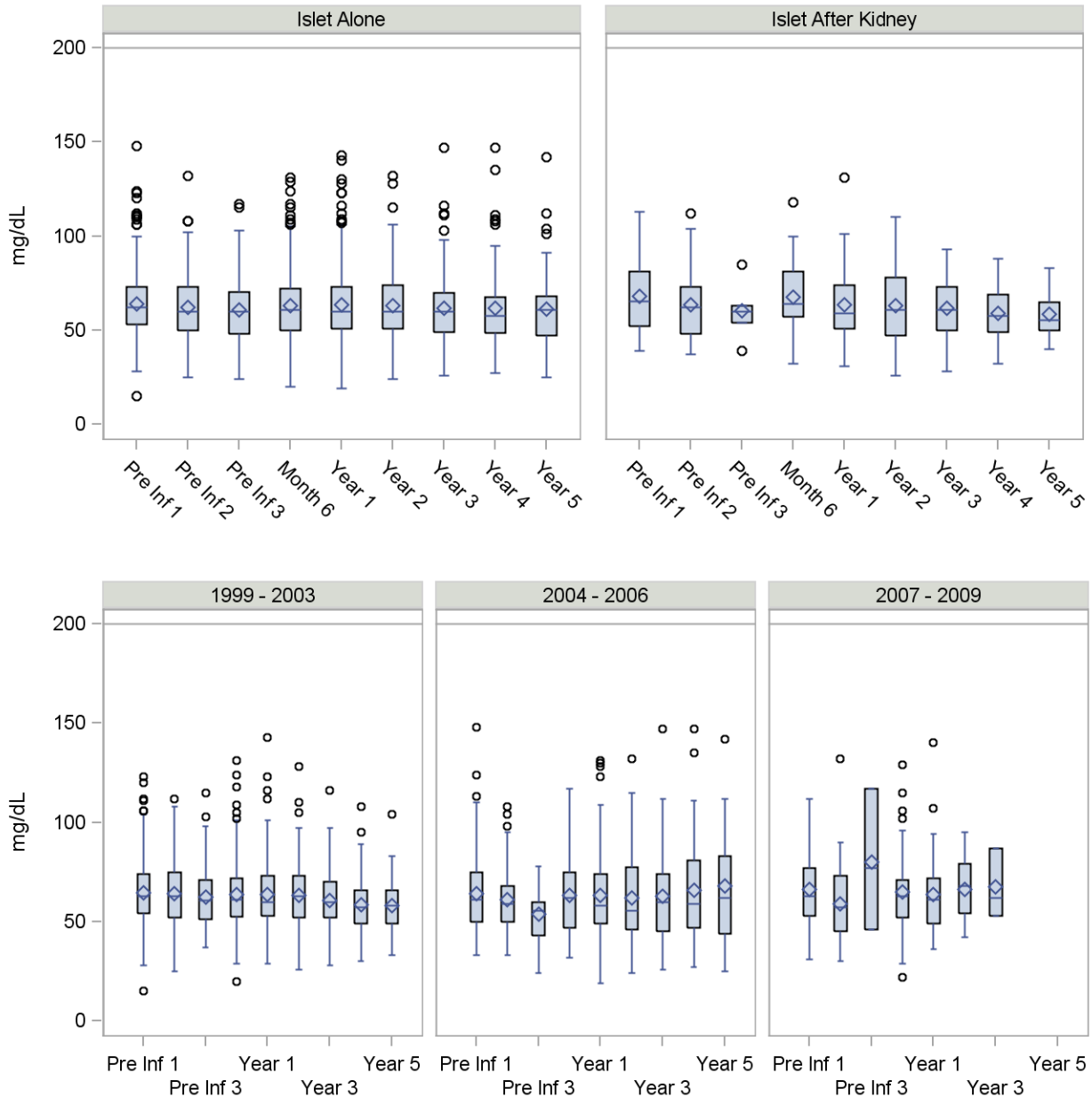
	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	397	270	86	266	263	162	120	83	47
Islet After Kidney	73	54	14	48	57	43	36	20	14
1999 - 2003	202	146	56	140	147	98	91	72	46
2004 - 2006	170	128	36	116	127	89	62	31	15
2007 - 2009	98	50	8	58	46	18	3	.	.

Exhibit 6-5
Total Cholesterol(mg/dL) by Infusion Type and Era



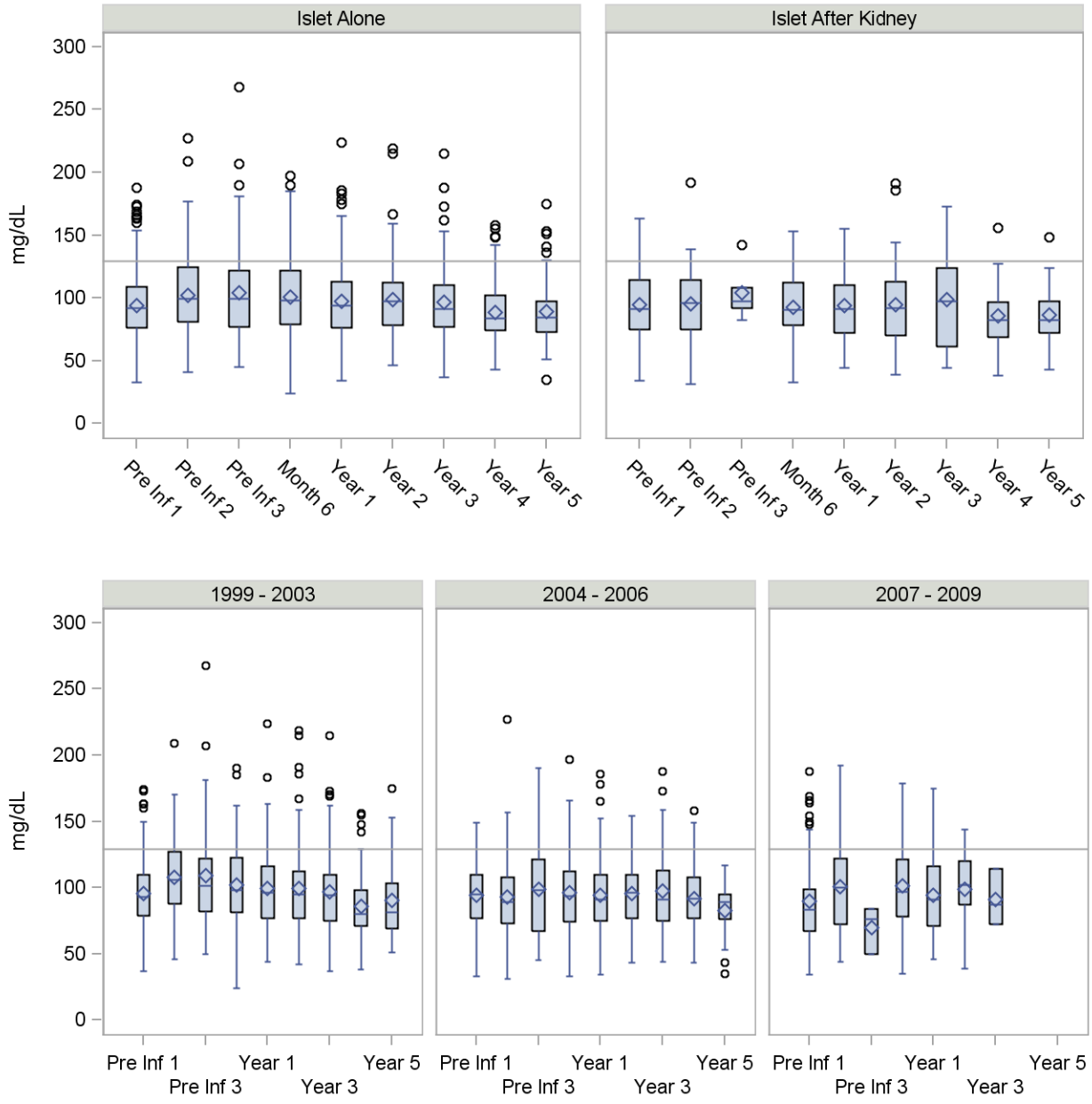
	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	394	231	80	274	291	173	130	90	60
Islet After Kidney	78	52	10	53	55	47	40	24	16
1999 - 2003	206	127	52	144	153	106	101	72	58
2004 - 2006	178	113	32	118	133	92	66	42	18
2007 - 2009	88	43	6	65	60	22	3	.	.

Exhibit 6-6
HDL(mg/dL) by Infusion Type and Era



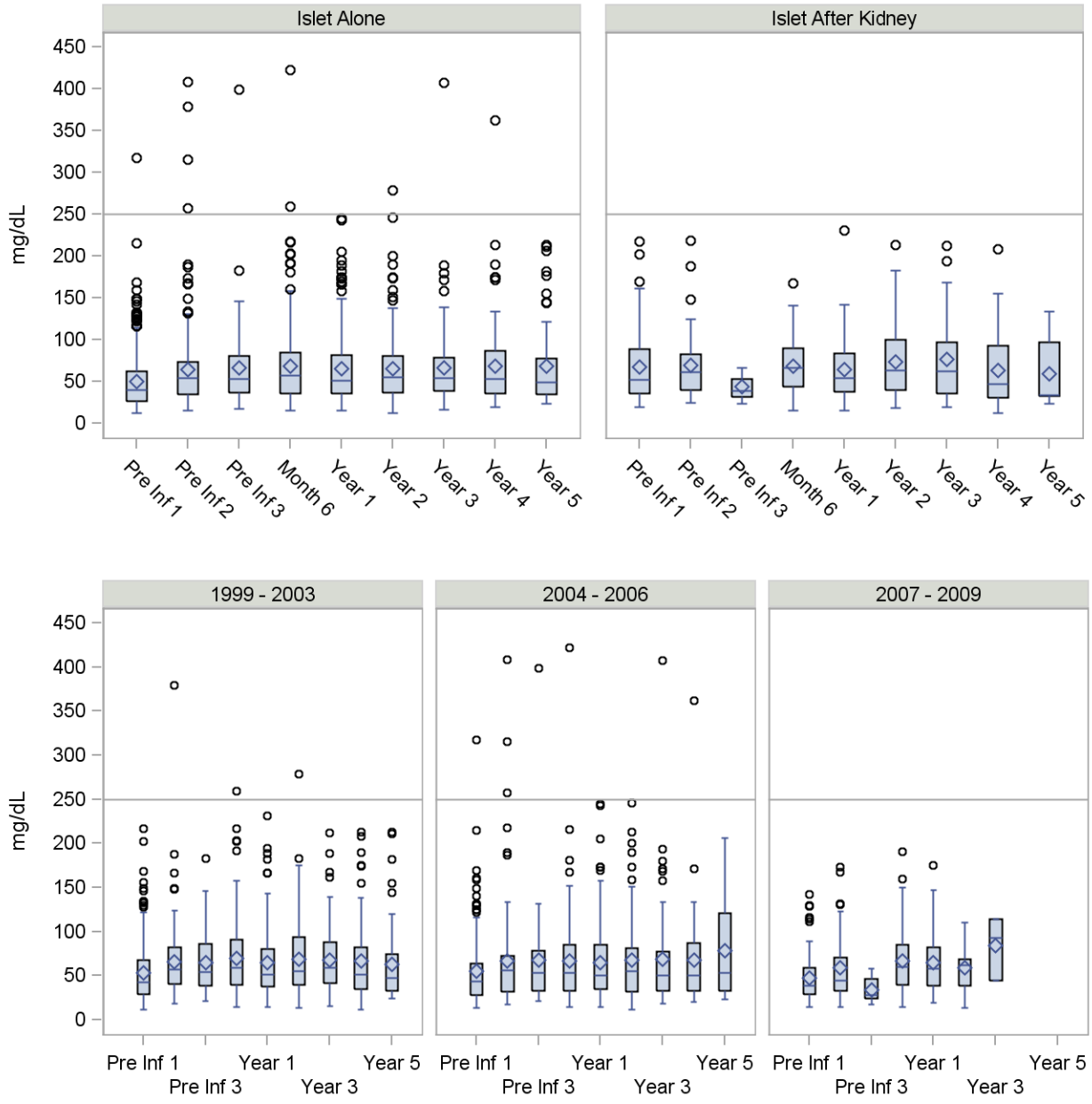
	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	379	211	68	252	275	161	123	84	59
Islet After Kidney	70	40	5	41	45	39	35	20	14
1999 - 2003	199	121	50	136	148	99	97	65	55
2004 - 2006	175	97	20	99	117	80	58	39	18
2007 - 2009	75	33	3	58	55	21	3	.	.

Exhibit 6-7
LDL(mg/dL) by Infusion Type and Era



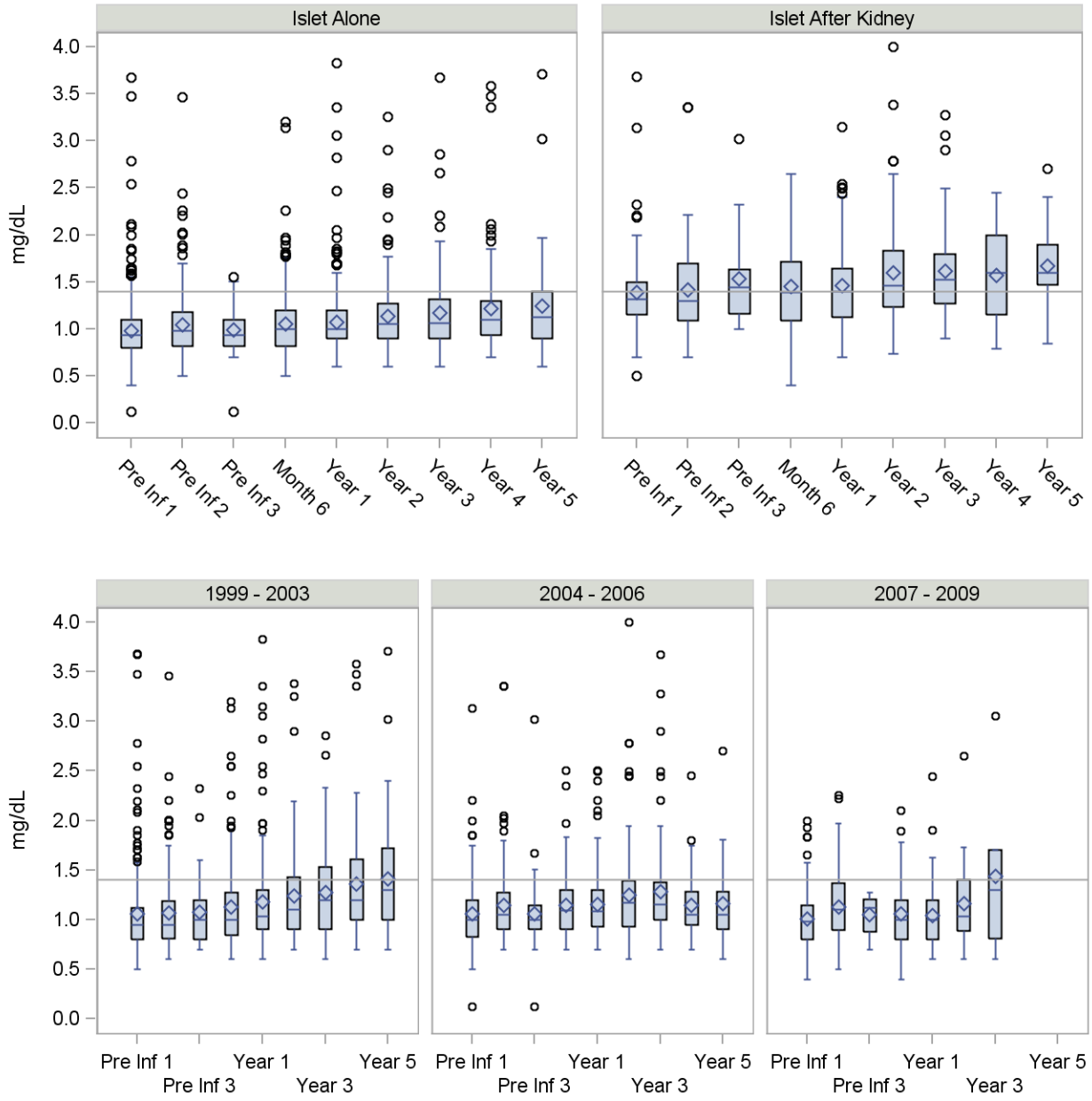
	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	361	208	66	247	269	160	121	85	58
Islet After Kidney	62	38	5	40	43	38	34	20	14
1999 - 2003	180	119	49	132	145	98	97	65	55
2004 - 2006	167	94	19	98	113	79	55	40	17
2007 - 2009	76	33	3	57	54	21	3	.	.

Exhibit 6-8
Triglycerides(mg/dL) by Infusion Type and Era



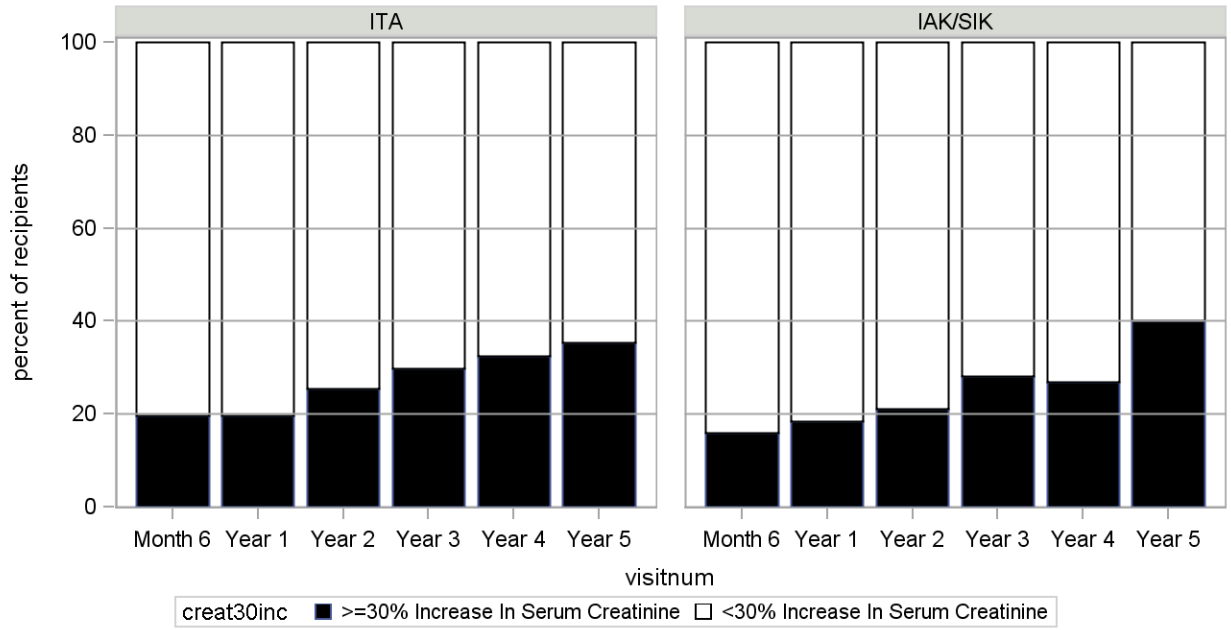
	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	394	228	80	271	290	172	130	90	59
Islet After Kidney	77	51	9	53	55	47	39	23	16
1999 - 2003	206	127	51	144	153	106	101	72	57
2004 - 2006	177	112	32	117	132	91	65	41	18
2007 - 2009	88	40	6	63	60	22	3	.	.

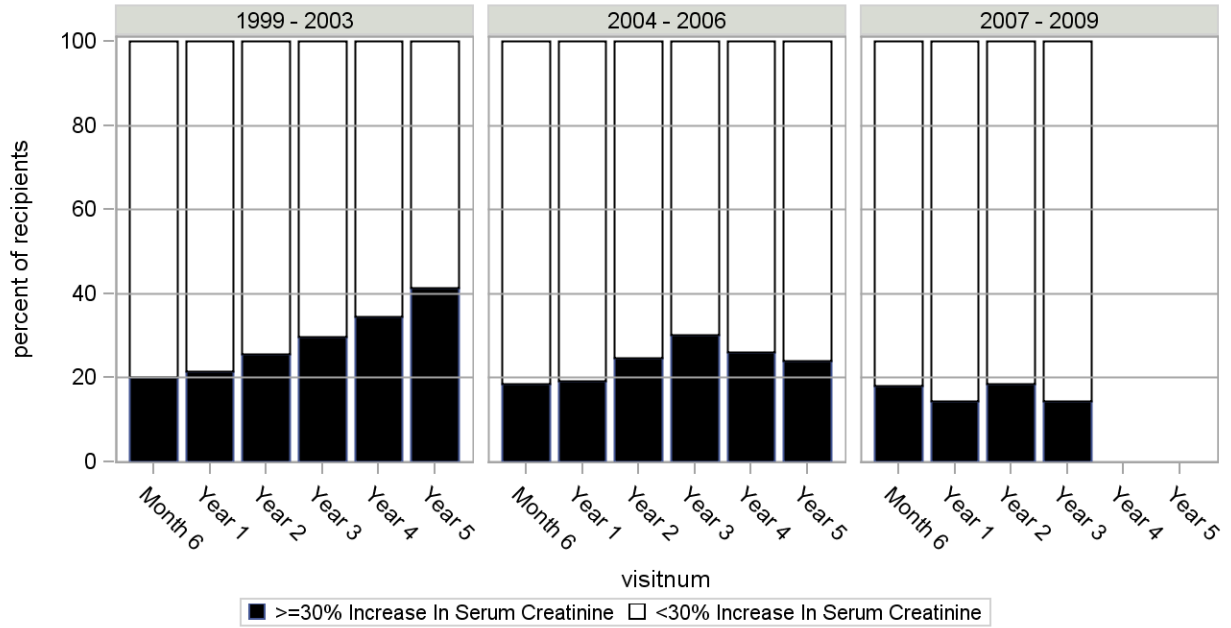
Exhibit 6-9
Serum Creatinine(mg/dL) by Infusion Type and Era



	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	431	291	90	318	308	198	149	109	69
Islet After Kidney	87	62	16	64	72	57	51	27	21
1999 - 2003	218	156	58	162	169	117	110	86	65
2004 - 2006	187	135	40	140	146	110	83	50	25
2007 - 2009	113	62	8	80	65	28	7	.	.

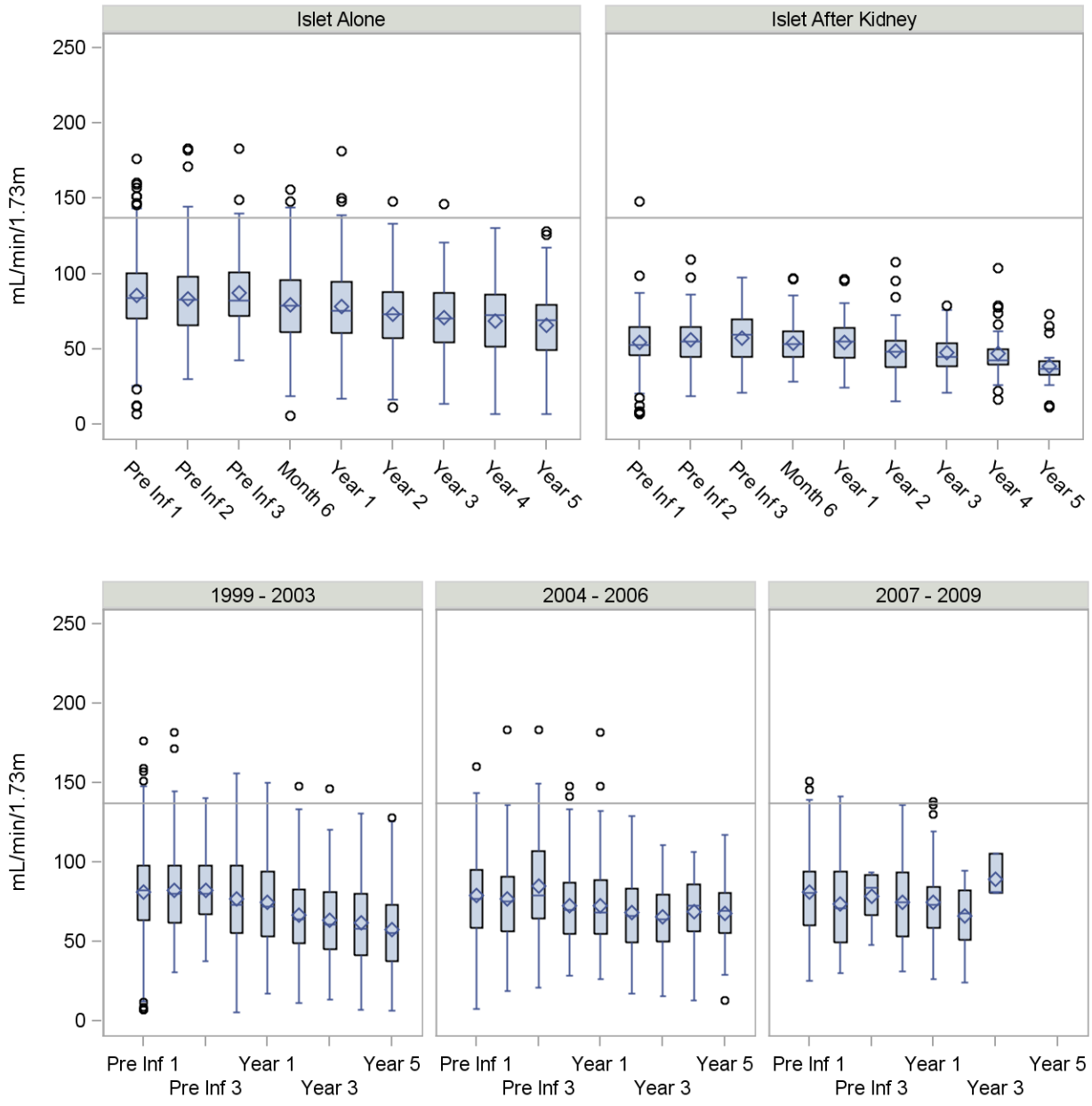
Exhibit 6-10
Percent of Recipients with a 30% increase in Serum Creatinine at each Follow-up Time Point by Infusion Type and Era





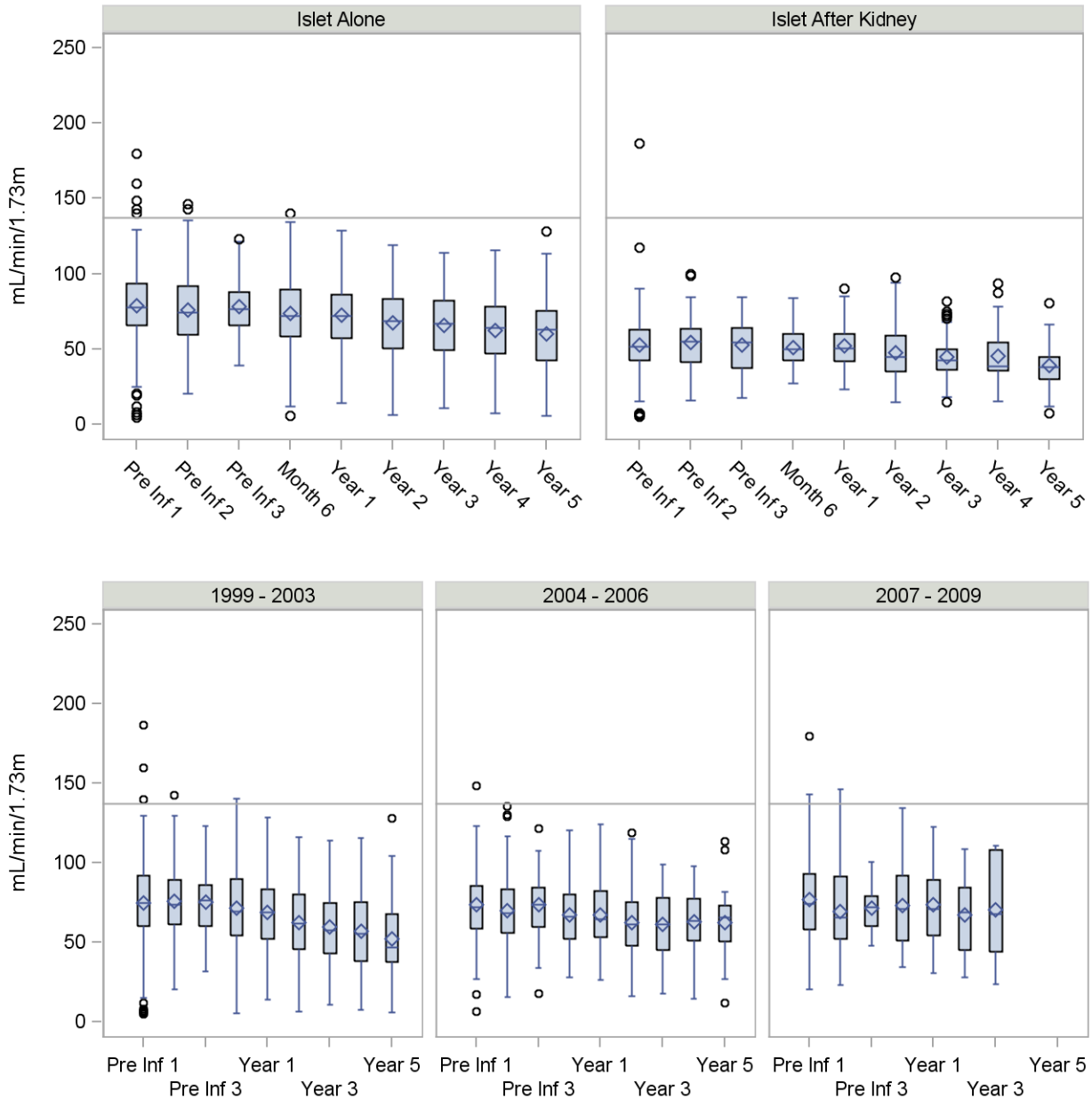
	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	315	306	197	148	108	68
Islet After Kidney	63	71	57	50	26	20
1999 - 2003	160	168	117	108	84	63
2004 - 2006	140	146	110	83	50	25
2007 - 2009	78	63	27	7	.	.

Exhibit 6-11
Cockgroft-Gault Calculated Clearance(mL/min/1.73m^2) by Infusion Type and Era



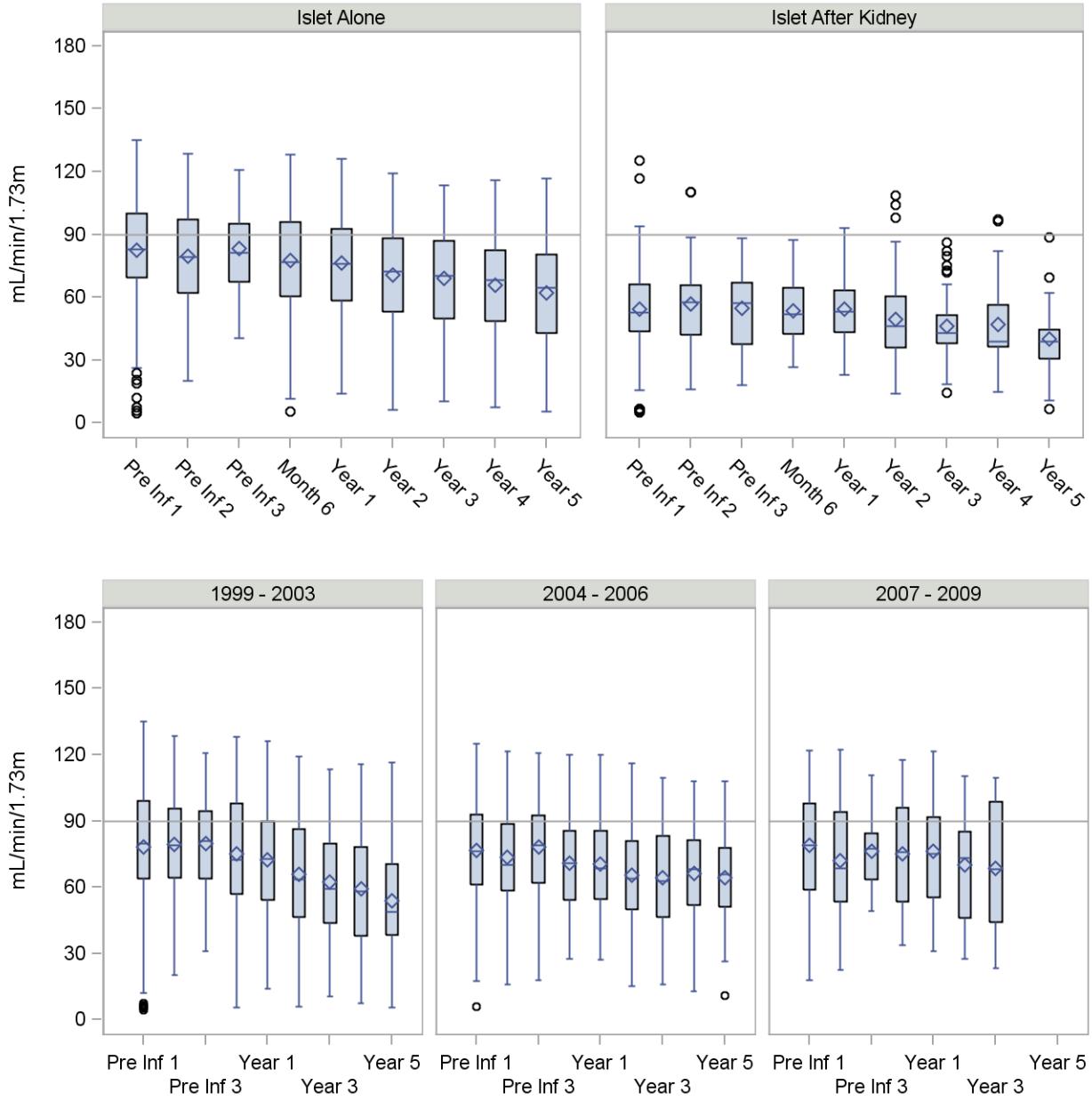
	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	418	281	86	304	290	179	138	100	61
Islet After Kidney	83	59	15	61	67	56	47	26	17
1999 - 2003	215	154	58	159	159	114	107	84	59
2004 - 2006	180	127	35	132	138	100	75	42	19
2007 - 2009	106	59	8	74	60	21	3	.	.

Exhibit 6-12
MDRD Estimated Creatinine Clearance (mL/min/1.73m^2) by Infusion Type and Era



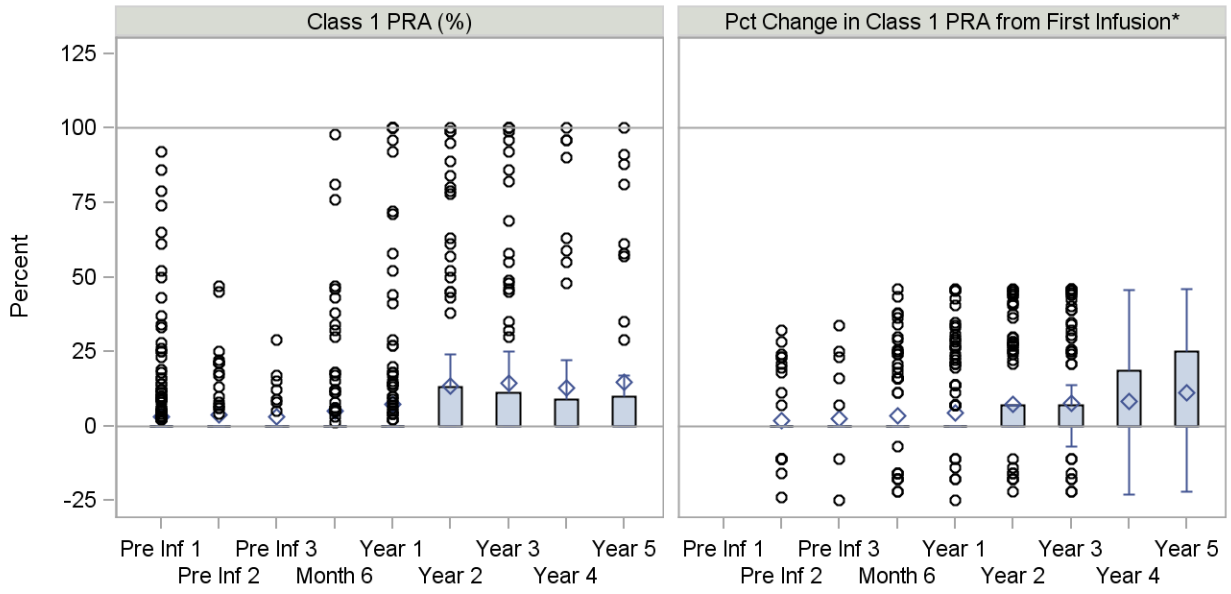
	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	430	291	90	318	306	197	148	109	68
Islet After Kidney	86	61	16	63	70	56	50	27	21
1999 - 2003	218	156	58	162	167	117	110	86	64
2004 - 2006	186	134	40	139	145	109	82	50	25
2007 - 2009	112	62	8	80	64	27	6	.	.

Exhibit 6-13
Chronic Kidney Disease Collaboration (CKD-EPI) Estimated GFR(mL/min/1.73m^2) by Infusion Type and Era



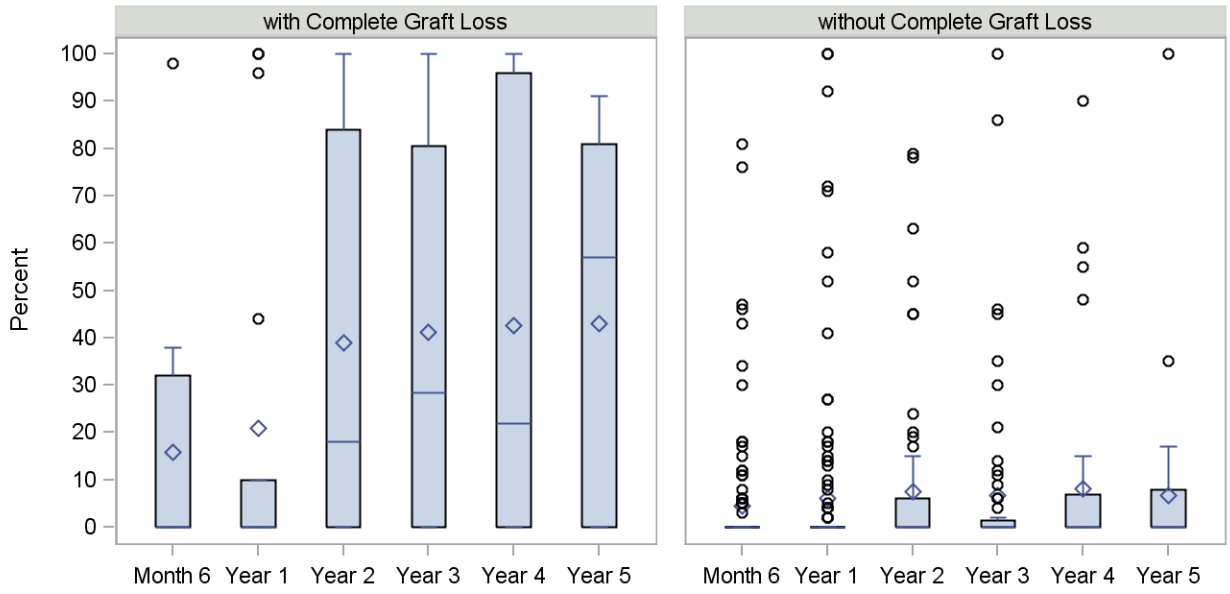
	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	430	291	90	318	306	197	148	109	68
Islet After Kidney	86	61	16	63	70	56	50	27	21
1999 - 2003	218	156	58	162	167	117	110	86	64
2004 - 2006	186	134	40	139	145	109	82	50	25
2007 - 2009	112	62	8	80	64	27	6	.	.

Exhibit 6-14
Class 1 PRA and its Percent Change from First Infusion



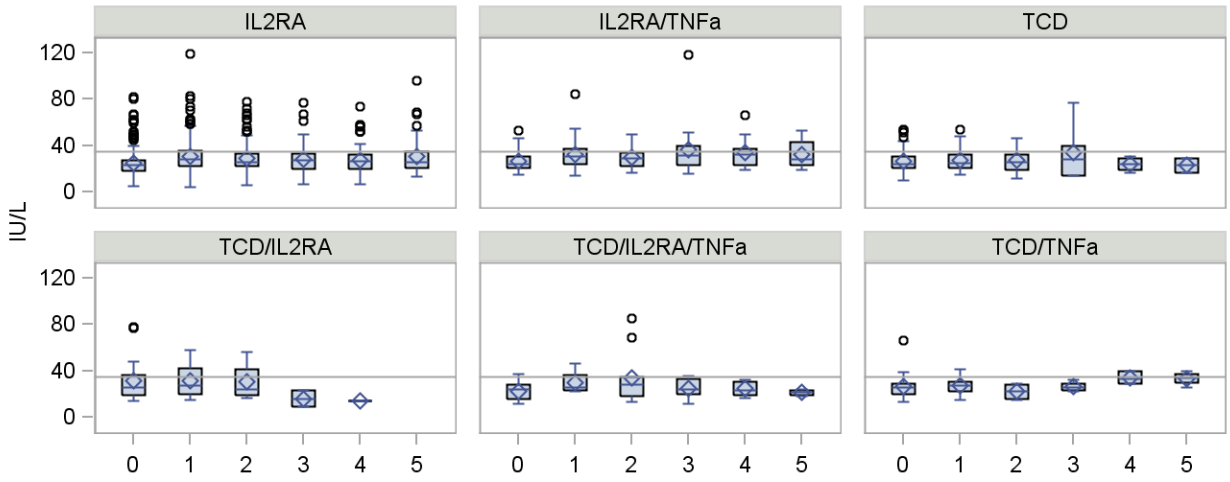
	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Class 1 PRA (%)	374	79	30	144	165	112	97	57	47
Pct Change in Class 1 PRA from First Infusion*	.	76	30	140	161	108	95	55	45

Exhibit 6-15
Class 1 PRA Post Last Infusion by Graft Loss for Islet Alone Recipients

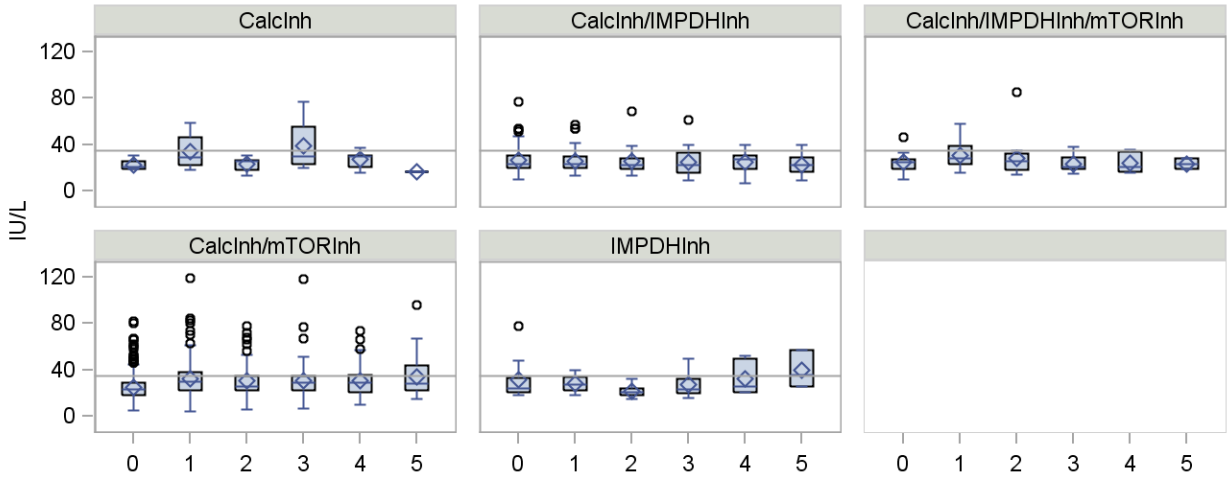


	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
with Complete Graft Loss	11	17	23	20	9	11
without Complete Graft Loss	122	135	70	64	39	31

Exhibit 6-16
AST (IU/L) by Immunosuppression Categories

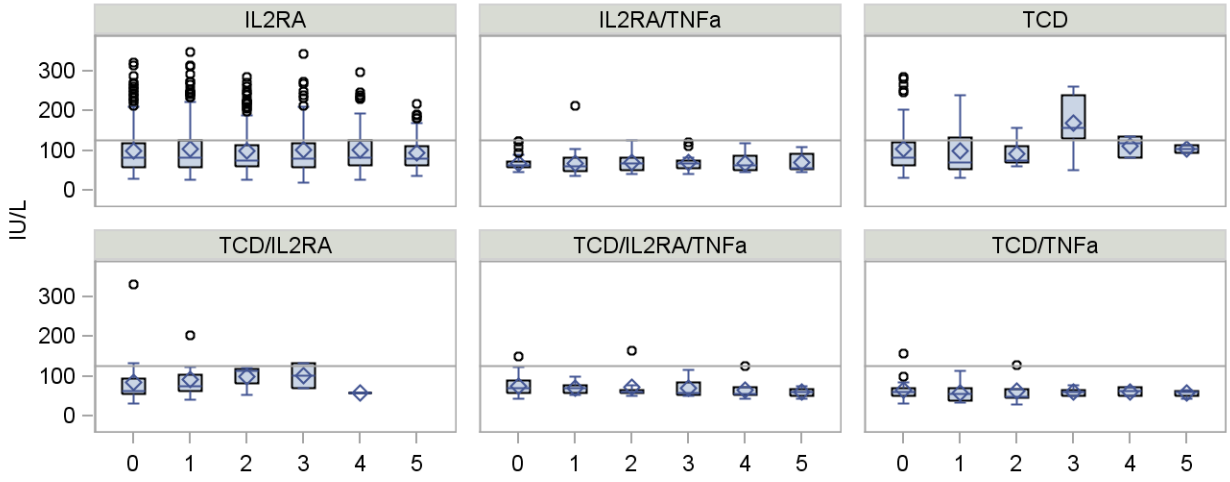


Ns	0	1	2	3	4	5
Induction						
IL2RA	241	194	136	115	79	46
IL2RA/TNFa	49	40	28	16	14	8
TCD	47	25	9	6	4	2
TCD/IL2RA	20	8	4	2	1	.
TCD/IL2RA/TNFa	28	12	10	9	7	4
TCD/TNFa	18	10	6	6	3	4

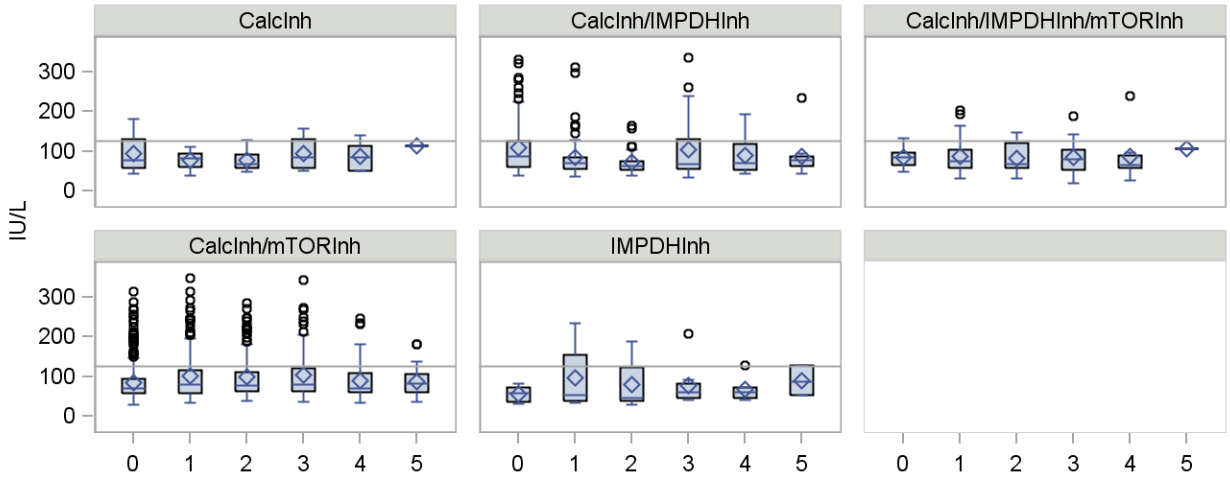


Ns	0	1	2	3	4	5
Maintenance						
CalcInh	4	9	8	4	6	1
CalcInh/IMPDHInh	64	46	27	25	21	14
CalcInh/IMPDHInh/mTORInh	13	33	17	14	8	2
CalcInh/mTORInh	342	169	109	91	52	27
IMPDHInh	10	8	8	8	6	3

Exhibit 6-17
Alkaline phosphatase (II/L) by Immunosuppression Categories

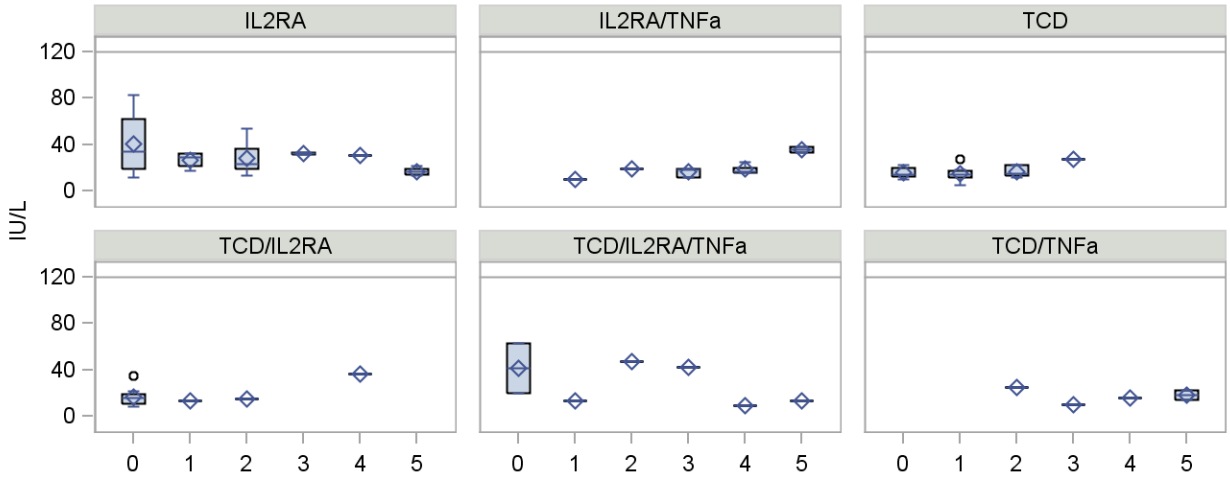


Ns	0	1	2	3	4	5
Induction						
IL2RA	235	193	132	113	77	45
IL2RA/TNFa	49	40	28	15	14	7
TCD	51	23	7	5	3	2
TCD/IL2RA	20	9	4	2	1	.
TCD/IL2RA/TNFa	29	12	9	8	7	4
TCD/TNFa	20	10	7	6	3	4

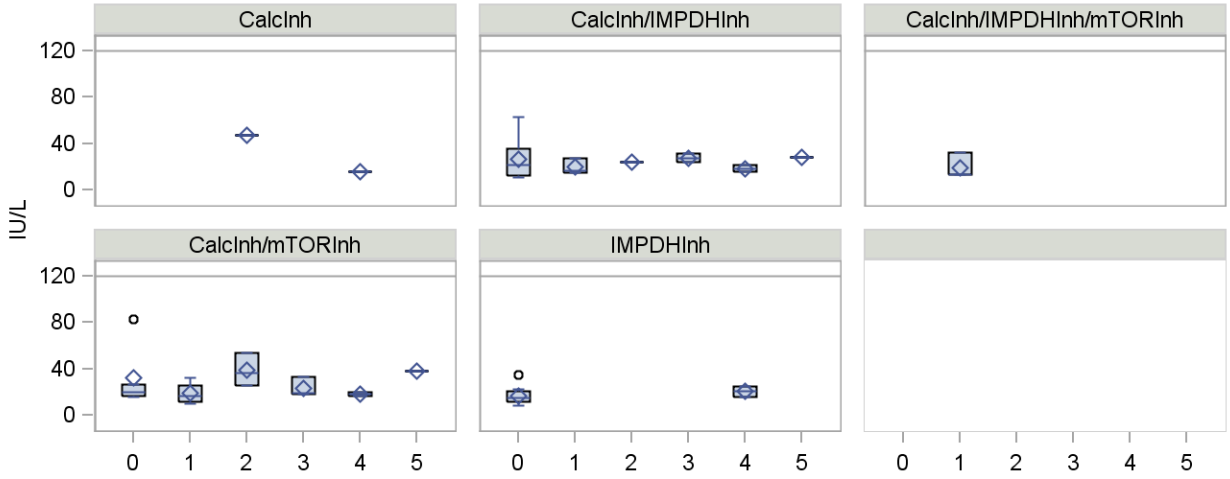


Ns	0	1	2	3	4	5
Maintenance						
CalcInh	4	9	8	4	6	1
CalcInh/IMPDHInh	72	48	29	23	18	11
CalcInh/IMPDHInh/mTORInh	13	32	15	14	8	1
CalcInh/mTORInh	334	169	106	90	52	28
IMPDHInh	10	8	8	8	6	3

Exhibit 6-18
BUN (IU/L) by Immunosuppression Categories

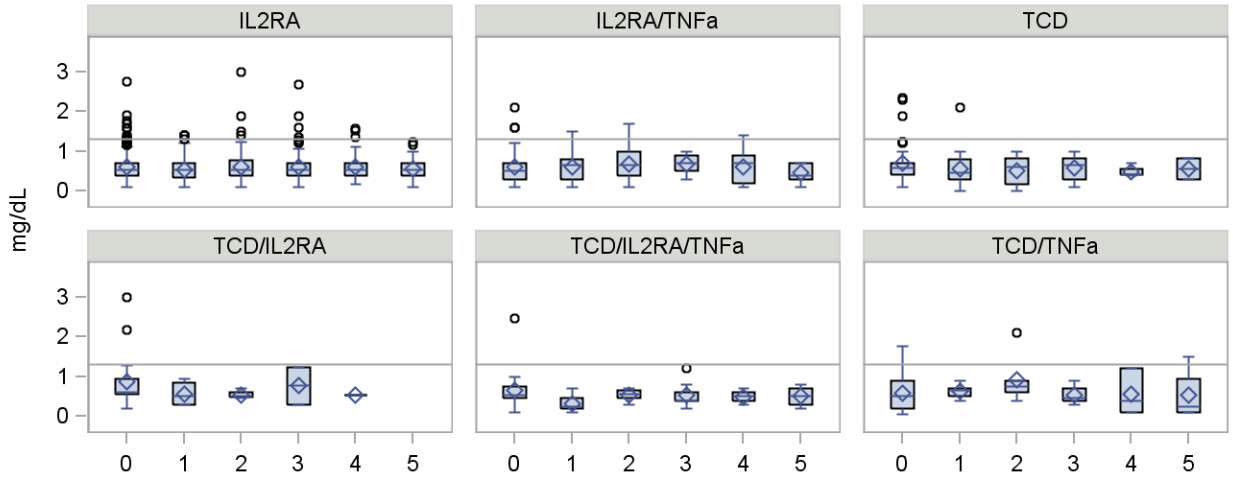


Ns	0	1	2	3	4	5
Induction						
IL2RA	4	4	6	2	1	4
IL2RA/TNFa	.	1	1	3	5	2
TCD	13	8	5	1	.	.
TCD/IL2RA	8	1	1	.	1	.
TCD/IL2RA/TNFa	2	1	1	1	1	1
TCD/TNFa	.	.	1	1	1	2

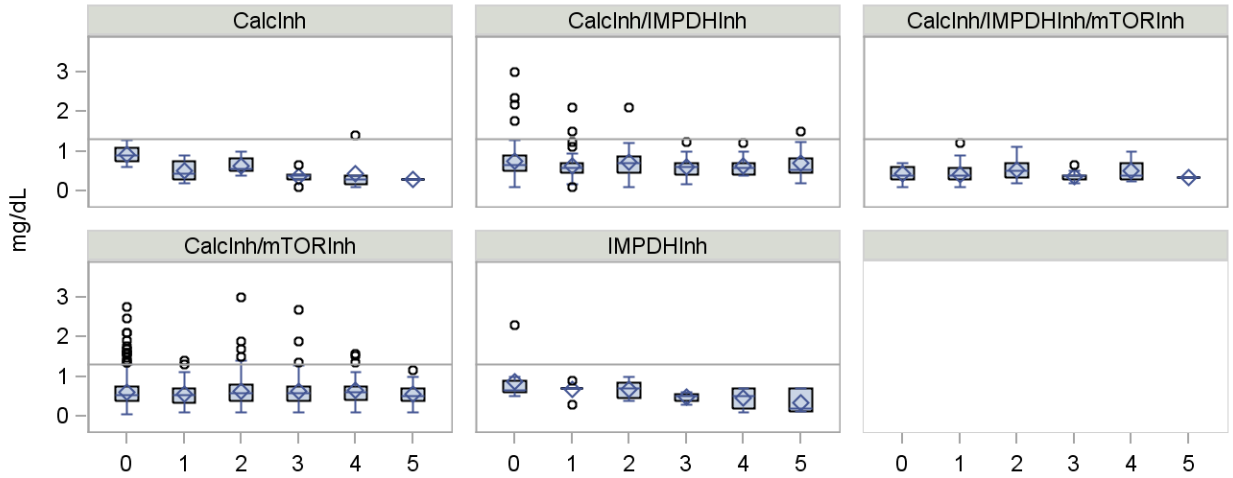


Ns	0	1	2	3	4	5
Maintenance						
CalcInh	.	.	1	.	1	.
CalcInh/IMPDHInh	13	3	1	2	2	1
CalcInh/IMPDHInh/mTORInh	.	3	.	.	.	.
CalcInh/mTORInh	5	6	3	3	2	1
IMPDHInh	12	.	.	.	2	.

Exhibit 6-19
Bilirubin (mg/dL) by Immunosuppression Categories

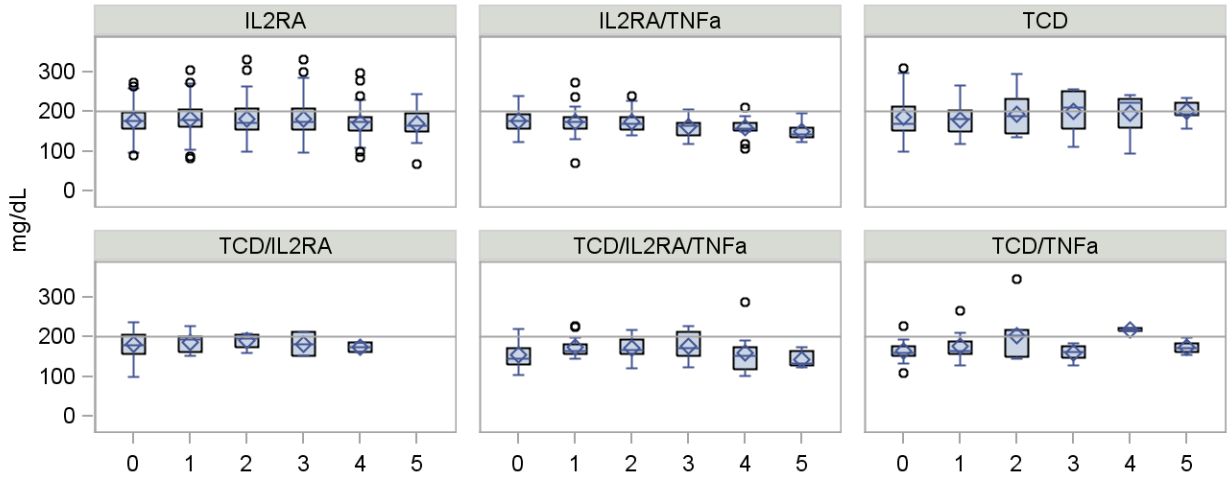


Ns	0	1	2	3	4	5
Induction						
IL2RA	240	179	128	106	65	38
IL2RA/TNFa	48	39	28	15	14	7
TCD	48	22	9	6	4	2
TCD/IL2RA	20	8	4	2	1	.
TCD/IL2RA/TNFa	29	12	8	8	7	4
TCD/TNFa	19	10	6	6	3	4

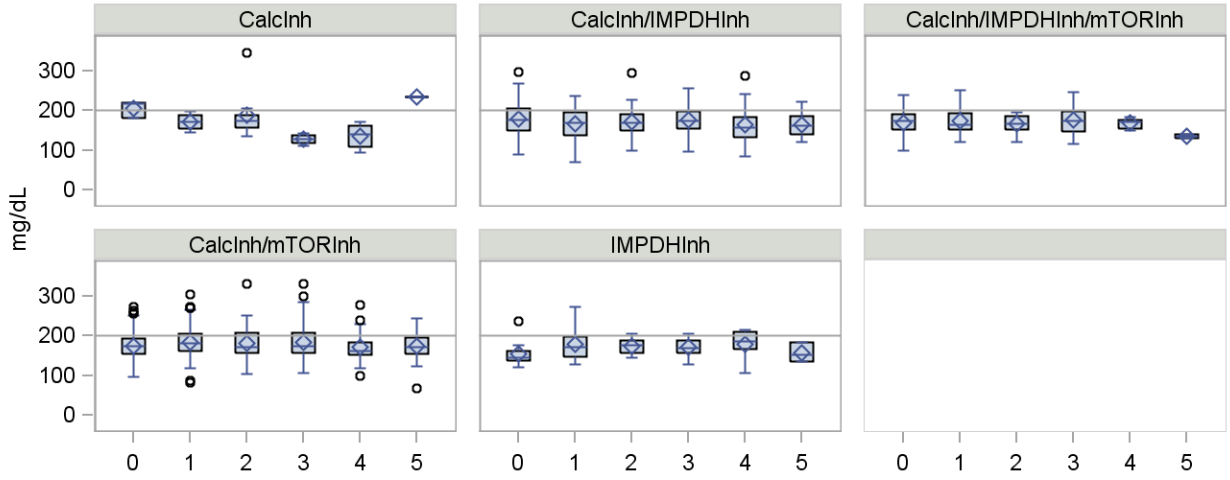


Ns	0	1	2	3	4	5
Maintenance						
CalcInh	4	8	6	5	6	1
CalcInh/IMPDHInh	68	48	27	23	18	11
CalcInh/IMPDHInh/mTORInh	13	33	16	13	8	1
CalcInh/mTORInh	336	155	105	81	45	24
IMPDHInh	10	6	8	8	6	3

Exhibit 6-20
Total cholesterol (mg/dL) by Immunosuppression Categories

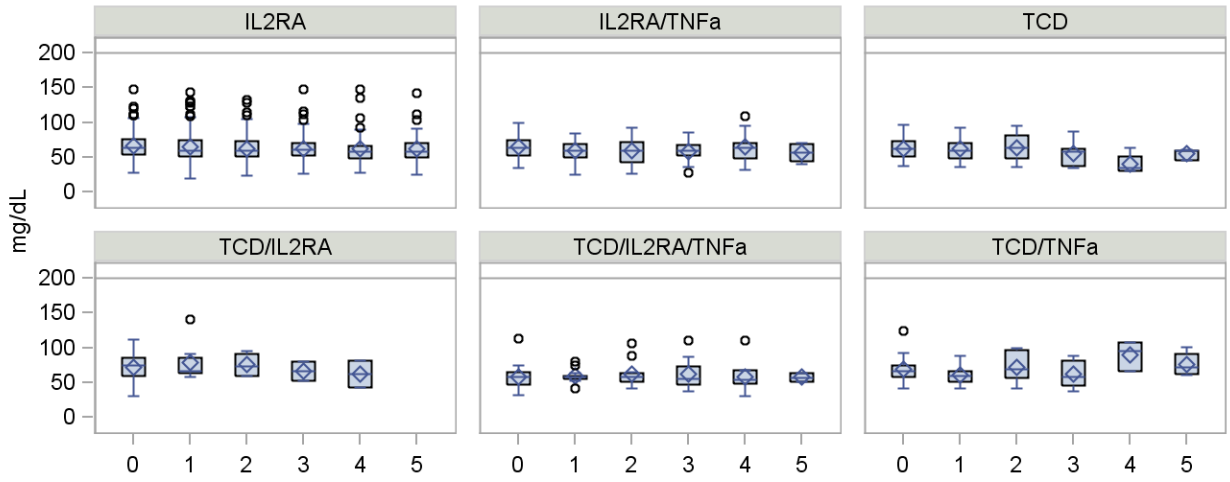


Ns	0	1	2	3	4	5
Induction						
IL2RA	247	194	133	118	72	48
IL2RA/TNFa	49	39	27	14	13	6
TCD	51	29	13	7	4	5
TCD/IL2RA	18	8	4	2	2	.
TCD/IL2RA/TNFa	29	14	13	12	11	6
TCD/TNFa	19	10	7	6	3	4

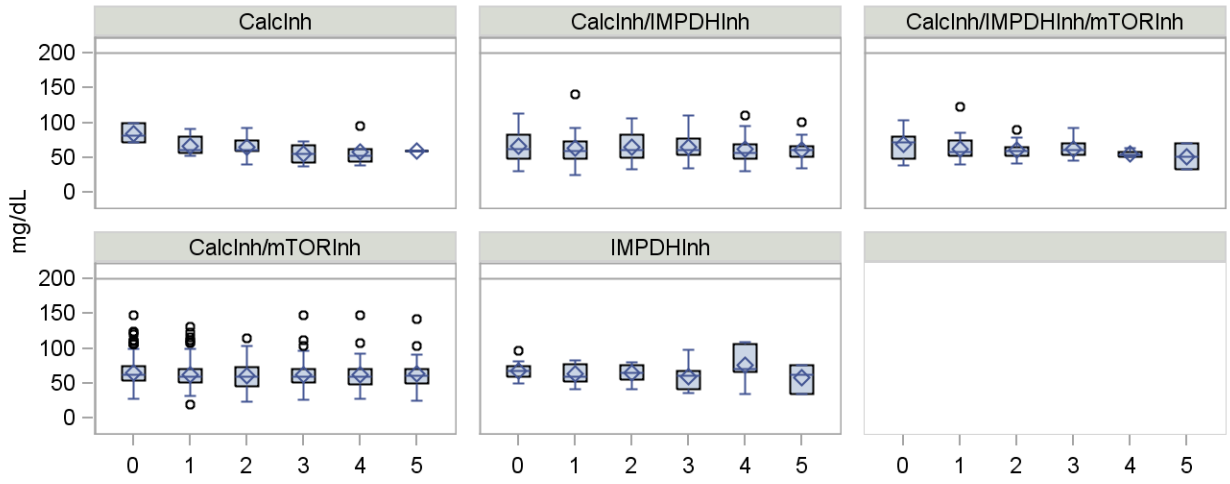


Ns	0	1	2	3	4	5
Maintenance						
CalcInh	3	10	9	4	6	1
CalcInh/IMPDHInh	65	51	28	26	21	16
CalcInh/IMPDHInh/mTORInh	14	34	18	17	7	2
CalcInh/mTORInh	344	172	110	91	49	30
IMPDHInh	13	8	8	8	6	3

Exhibit 6-21
HDL (mg/dL) by Immunosuppression Categories

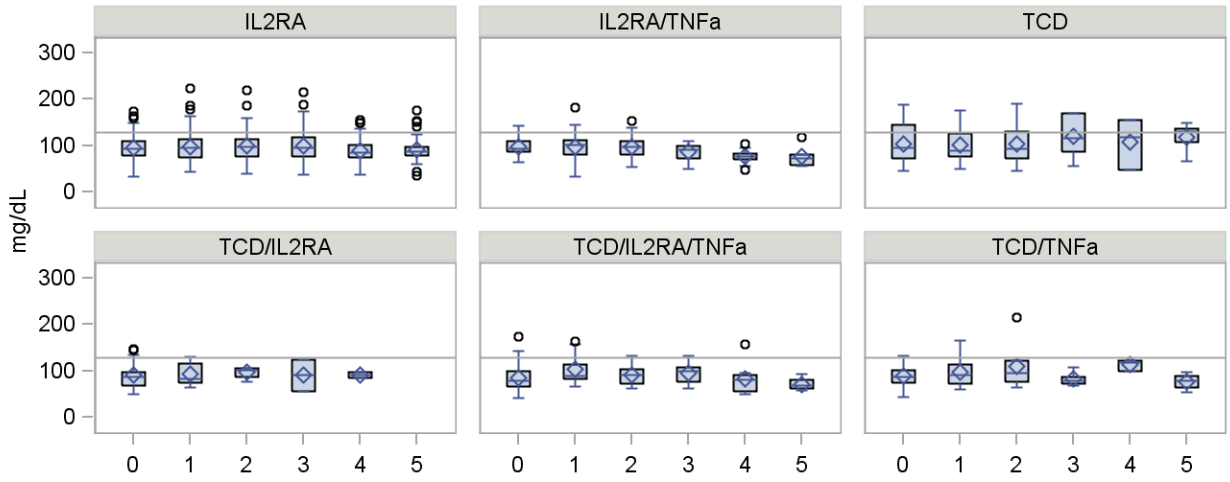


Ns	0	1	2	3	4	5
Induction						
IL2RA	236	171	118	107	64	46
IL2RA/TNFa	49	40	27	14	13	6
TCD	40	27	12	7	4	5
TCD/IL2RA	17	8	4	2	2	.
TCD/IL2RA/TNFa	29	14	12	12	11	6
TCD/TNFa	19	10	7	6	3	4

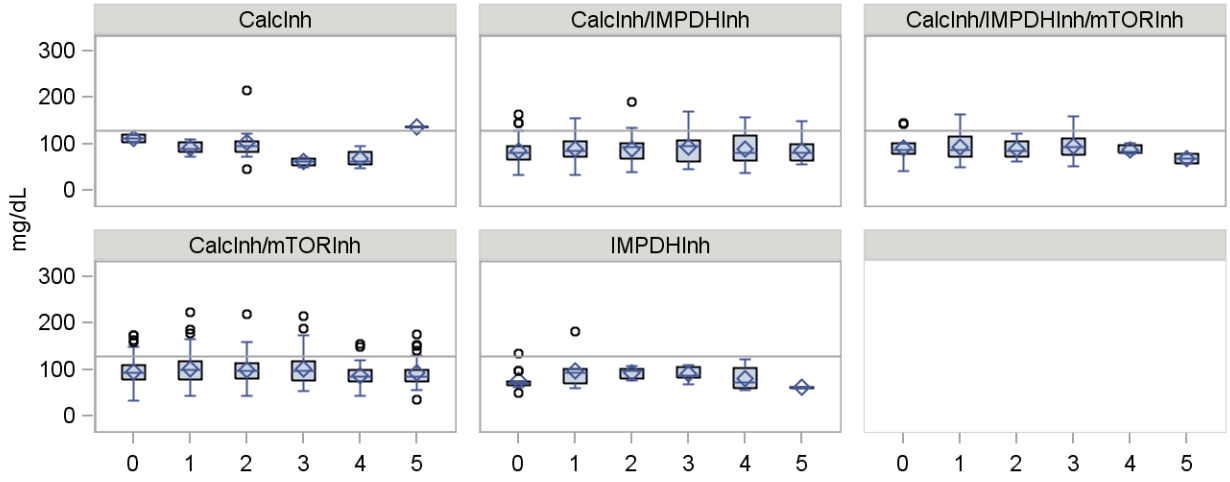


Ns	0	1	2	3	4	5
Maintenance						
CalcInh	3	10	9	4	6	1
CalcInh/IMPDHInh	52	45	26	24	19	15
CalcInh/IMPDHInh/mTORInh	13	34	17	17	7	2
CalcInh/mTORInh	336	153	97	81	43	29
IMPDHInh	12	8	8	8	6	3

Exhibit 6-22
LDL (mg/dL) by Immunosuppression Categories

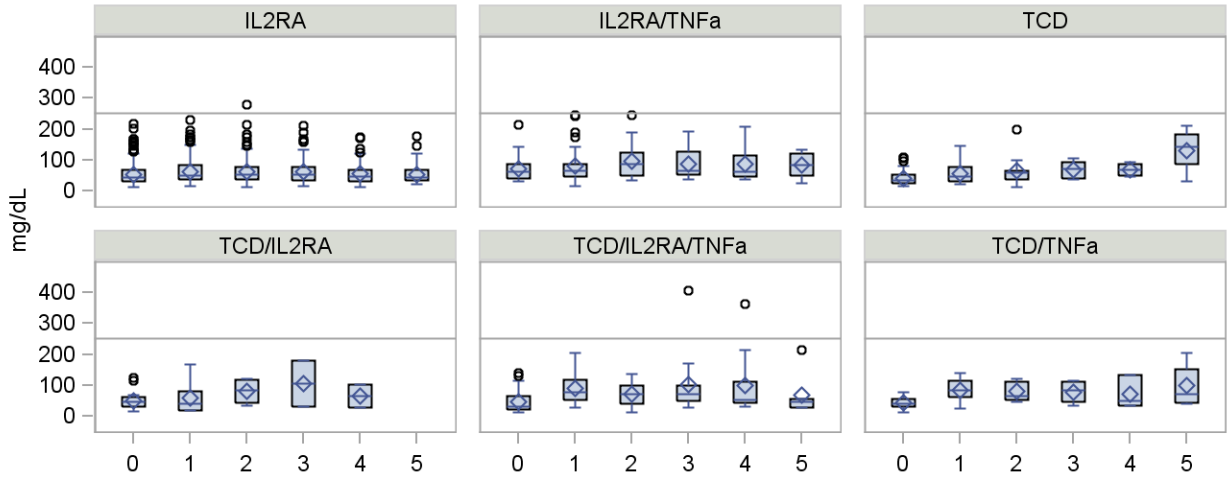


Ns	0	1	2	3	4	5
Induction						
IL2RA	220	166	116	106	66	45
IL2RA/TNFa	49	40	27	14	13	6
TCD	37	25	11	6	3	5
TCD/IL2RA	17	8	4	2	2	.
TCD/IL2RA/TNFa	29	14	12	11	11	6
TCD/TNFa	19	10	7	6	3	4

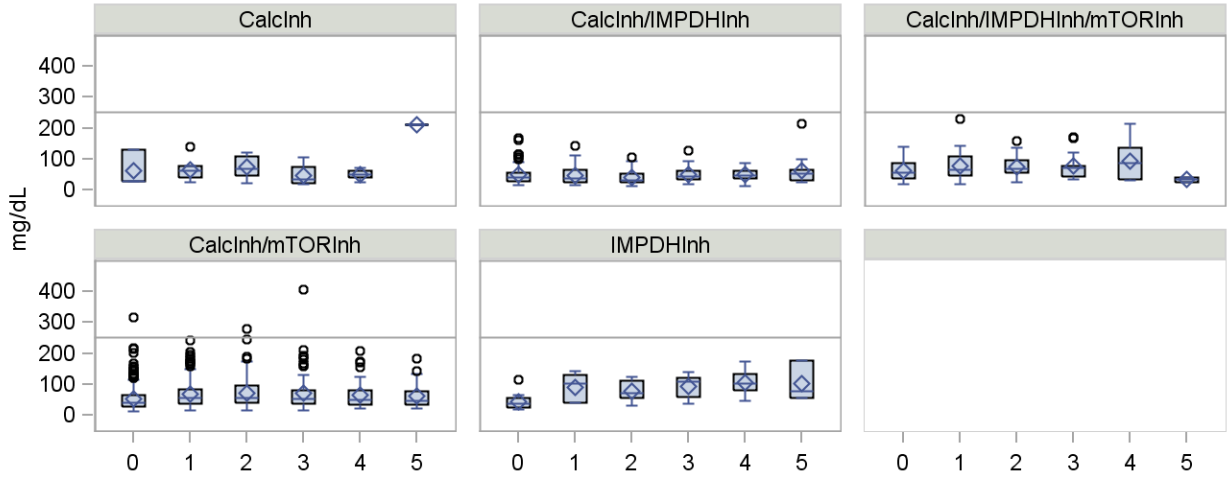


Ns	0	1	2	3	4	5
Maintenance						
CalcInh	2	9	9	4	6	1
CalcInh/IMPDHInh	43	42	26	23	19	15
CalcInh/IMPDHInh/mTORInh	13	34	17	17	7	2
CalcInh/mTORInh	325	151	95	80	43	29
IMPDHInh	13	8	8	8	6	2

Exhibit 6-23
Triglycerides (mg/dL) by Immunosuppression Categories

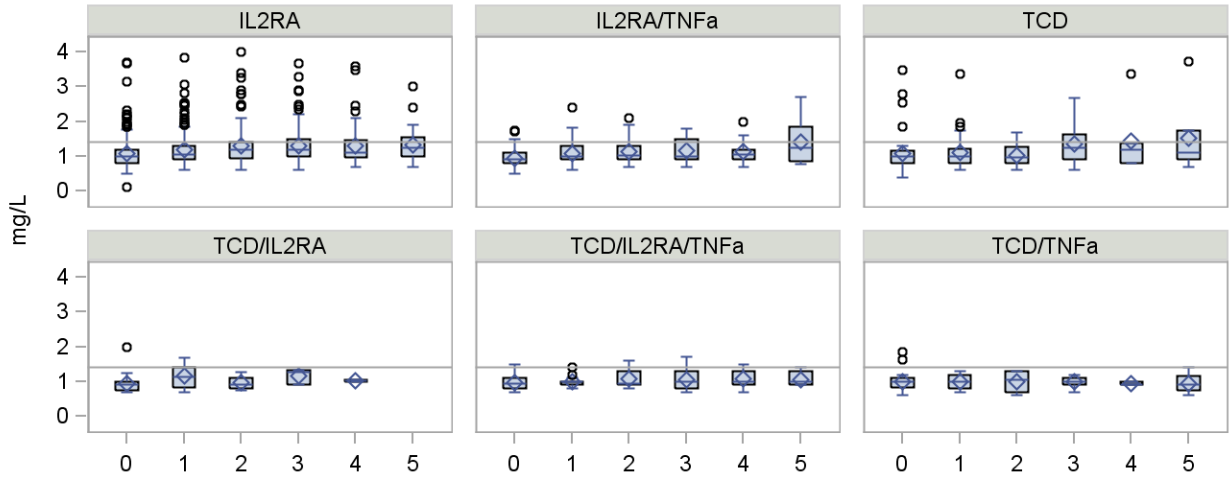


Ns	0	1	2	3	4	5
Induction						
IL2RA	246	192	132	117	72	48
IL2RA/TNFa	49	40	27	14	13	6
TCD	51	29	13	7	4	5
TCD/IL2RA	18	8	4	2	2	.
TCD/IL2RA/TNFa	29	14	13	12	11	6
TCD/TNFa	19	10	7	6	3	4

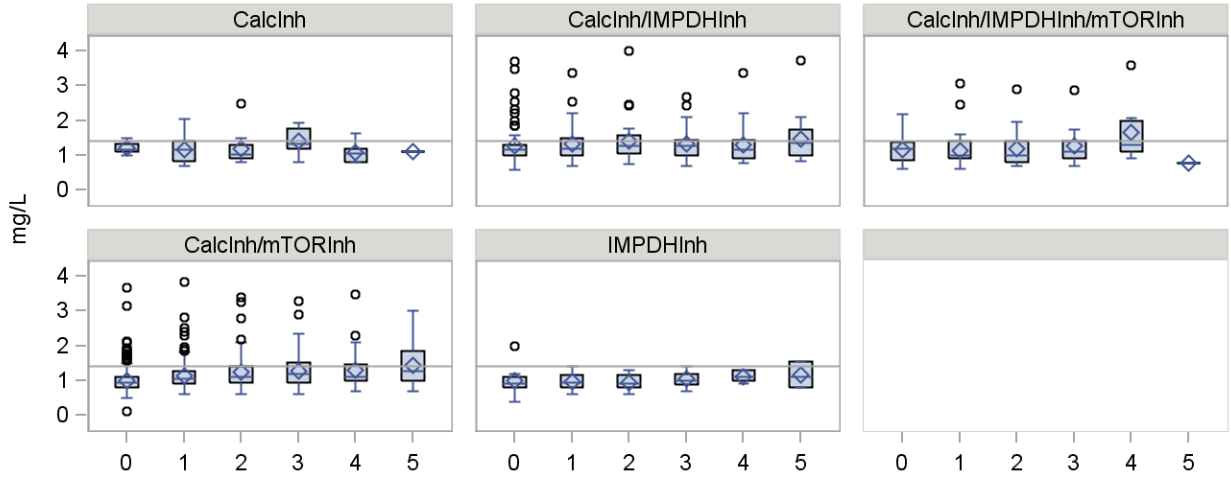


Ns	0	1	2	3	4	5
Maintenance						
CalcInh	3	10	9	4	6	1
CalcInh/IMPDHInh	65	51	28	26	20	16
CalcInh/IMPDHInh/mTORInh	14	34	18	17	7	2
CalcInh/mTORInh	343	171	109	90	49	30
IMPDHInh	13	8	8	8	6	3

Exhibit 6-24
Serum creatinine (mg/L) by Immunosuppression Categories

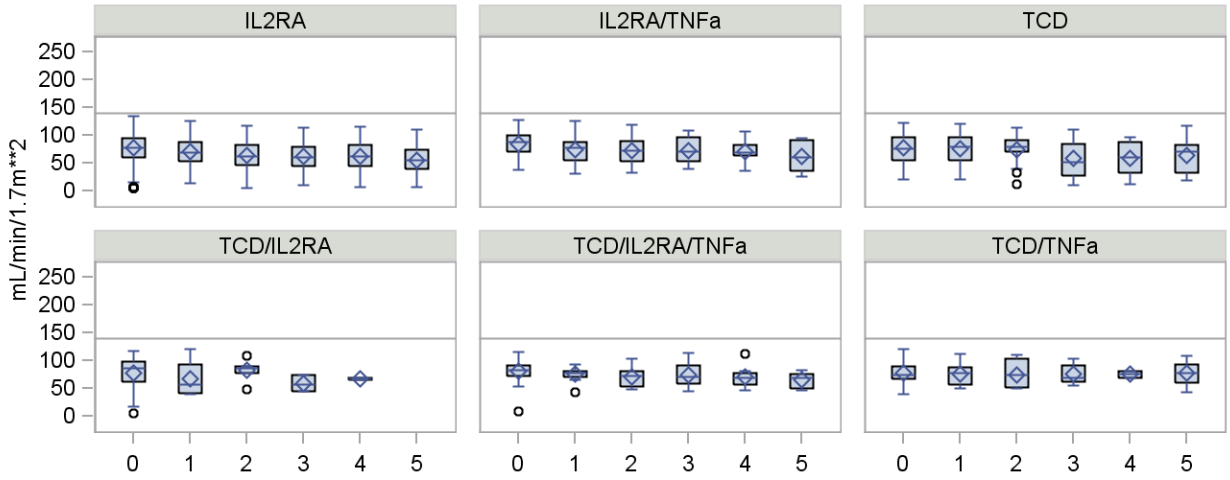


Ns	0	1	2	3	4	5
Induction						
IL2RA	266	212	151	133	85	55
IL2RA/TNFa	49	41	32	17	14	8
TCD	57	36	19	11	8	7
TCD/IL2RA	20	10	5	3	2	.
TCD/IL2RA/TNFa	29	13	14	13	11	7
TCD/TNFa	20	10	7	6	3	4

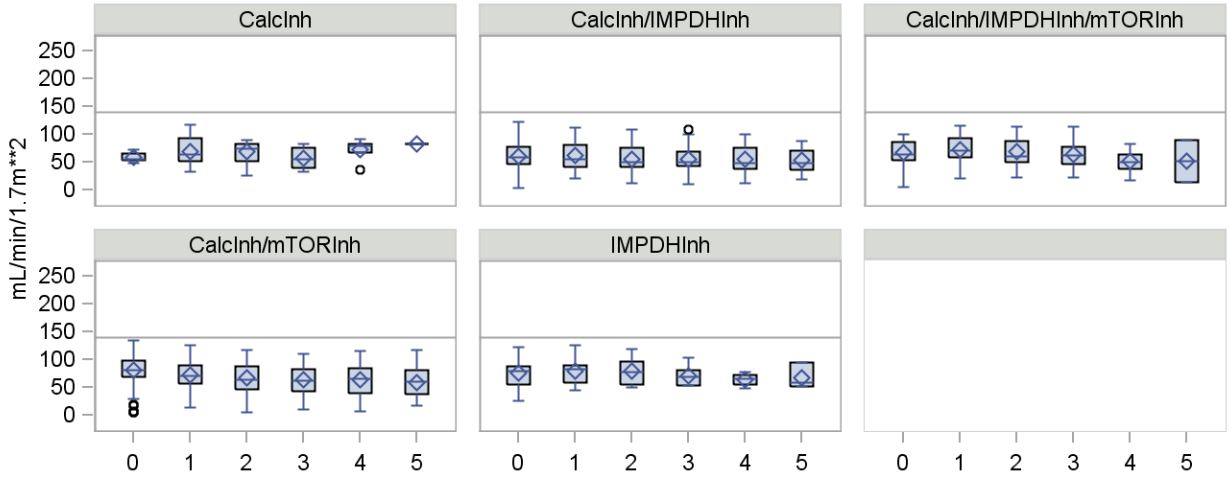


Ns	0	1	2	3	4	5
Maintenance						
CalcInh	5	11	10	6	6	1
CalcInh/IMPDHInh	75	55	36	30	27	18
CalcInh/IMPDHInh/mTORInh	18	35	22	17	9	2
CalcInh/mTORInh	360	187	125	104	59	35
IMPDHInh	13	8	8	8	6	3

Exhibit 6-25
CKD-EPI-GFR (mL/min/1.7m**2) by Immunosuppression Categories

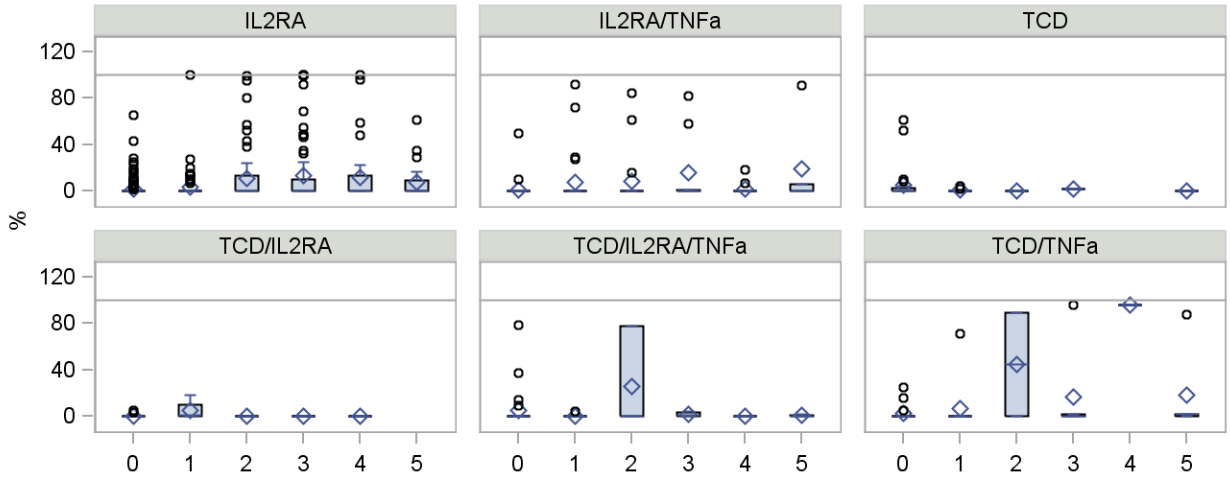


Ns	0	1	2	3	4	5
Induction						
IL2RA	265	211	150	132	85	55
IL2RA/TNFa	49	41	32	17	14	8
TCD	57	36	19	11	8	7
TCD/IL2RA	20	10	5	3	2	.
TCD/IL2RA/TNFa	29	13	14	13	11	7
TCD/TNFa	20	10	7	6	3	4

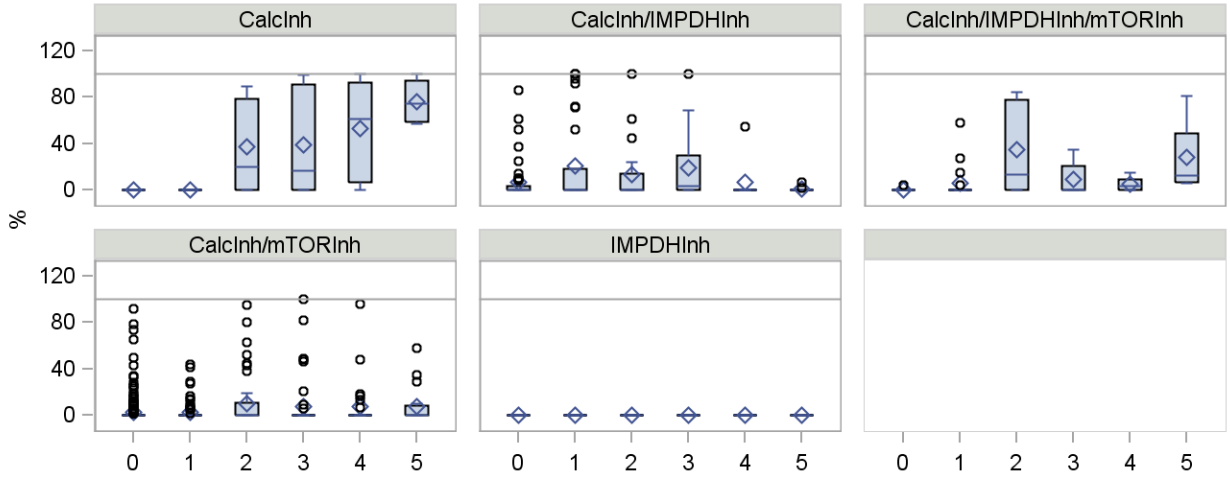


Ns	0	1	2	3	4	5
Maintenance						
CalcInh	5	11	10	6	6	1
CalcInh/IMPDHInh	75	55	36	30	27	18
CalcInh/IMPDHInh/mTORInh	17	35	22	17	9	2
CalcInh/mTORInh	360	186	124	104	59	35
IMPDHInh	13	8	8	8	6	3

Exhibit 6-26
Class 1 PRA (%) by Immunosuppression Categories

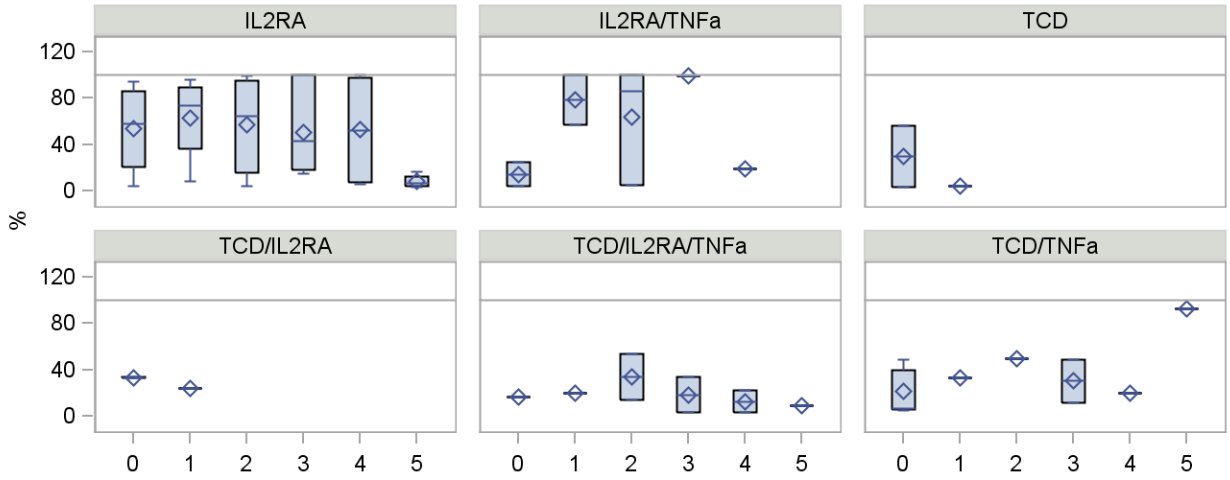


Ns	0	1	2	3	4	5
Induction						
IL2RA	190	74	62	64	34	26
IL2RA/TNFa	48	28	20	9	12	5
TCD	28	10	6	1	.	1
TCD/IL2RA	18	4	1	1	1	.
TCD/IL2RA/TNFa	29	13	3	4	3	4
TCD/TNFa	20	10	2	6	1	5

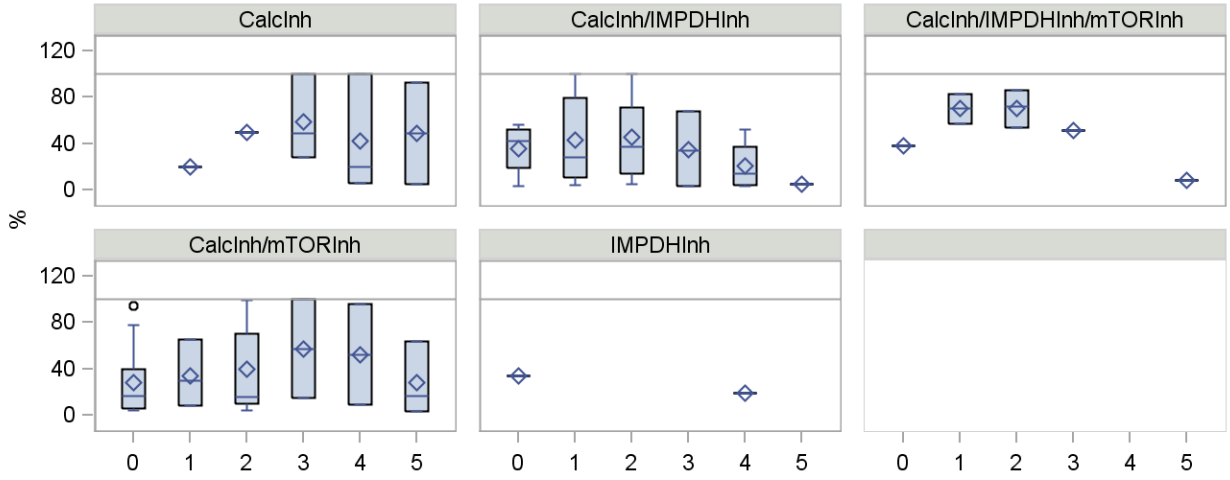


Ns	0	1	2	3	4	5
Maintenance						
CalcInh	1	5	5	8	8	4
CalcInh/IMPDHInh	49	31	20	16	8	10
CalcInh/IMPDHInh/mTORInh	12	19	7	8	6	4
CalcInh/mTORInh	299	80	51	49	26	20
IMPDHInh	9	4	2	5	3	1

Exhibit 6-27
Class 2 PRA (%) by Immunosuppression Categories

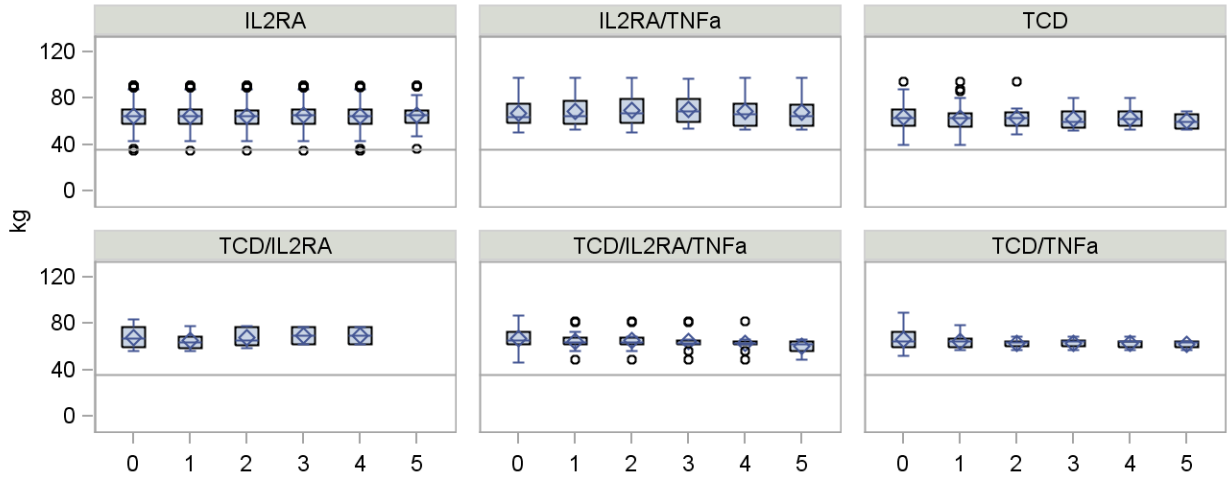


Ns	0	1	2	3	4	5
Induction						
IL2RA	4	4	6	7	4	4
IL2RA/TNFa	2	2	3	1	1	.
TCD	2	1	.	.	.	.
TCD/IL2RA	2	1	.	.	.	.
TCD/IL2RA/TNFa	1	1	2	2	2	1
TCD/TNFa	5	1	1	2	1	1

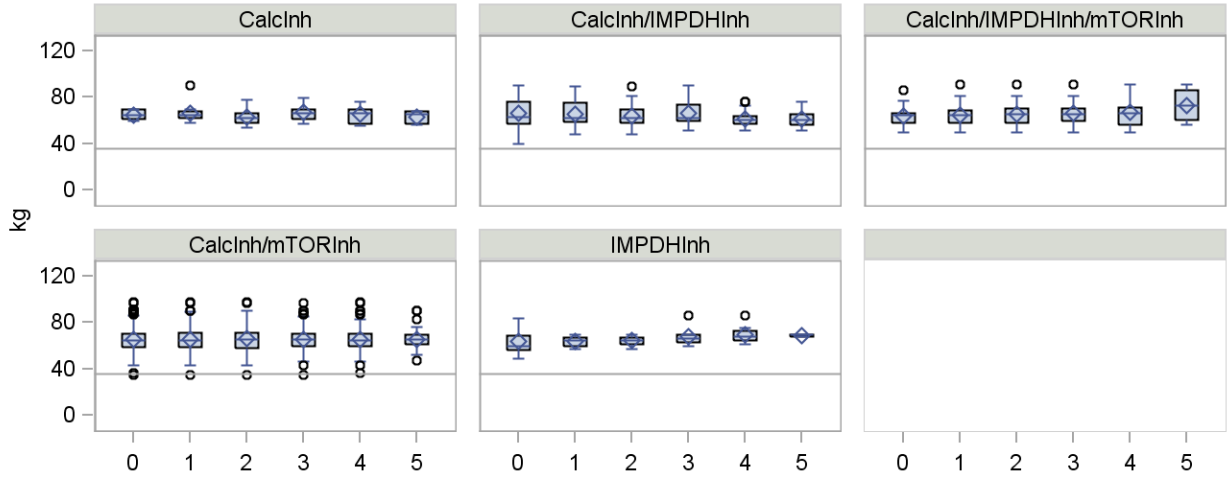


Ns	0	1	2	3	4	5
Maintenance						
CalcInh	.	1	1	3	3	2
CalcInh/IMPDHInh	4	8	5	3	4	1
CalcInh/IMPDHInh/mTORInh	1	2	3	1	.	1
CalcInh/mTORInh	15	3	5	2	2	3
IMPDHInh	1	.	.	.	1	.

Exhibit 6-28
Recipient body weight (kg) by Immunosuppression Categories



Ns	0	1	2	3	4	5
Induction						
IL2RA	259	210	175	153	112	67
IL2RA/TNFa	49	40	31	22	19	12
TCD	55	40	17	13	10	7
TCD/IL2RA	18	10	6	2	2	.
TCD/IL2RA/TNFa	29	18	15	13	12	7
TCD/TNFa	22	12	9	8	6	5



Ns	0	1	2	3	4	5
Maintenance						
CalcInh	6	11	11	9	11	6
CalcInh/IMPDHInh	79	61	44	41	28	20
CalcInh/IMPDHInh/mTORInh	18	37	25	22	11	4
CalcInh/mTORInh	352	184	142	116	74	43
IMPDHInh	10	7	9	8	8	3

Chapter 7
Adverse Events

In the first 30 days following islet transplantation, about 35-40% of recipients experienced a reportable adverse event (Exhibit 7-1A), which occurred less frequently in IAK/SIK than ITA. Many of these events were adjudicated by the local investigator as possibly to definitely related to either the infusion procedure or the immunosuppression (IS). The vast majority were not unexpected, such as abnormal lymphocyte count and liver function. Very few were infections. The instances of peritoneal hemorrhage seen in the early era 1999-2003 have been drastically reduced in the recent eras. About 20% of all recipients experience a serious adverse event in the first 30 days (Exhibit 7-1B), which occurred about equally in IAK/SIK as in ITA, but have declined somewhat over the eras.

In the first year after islet transplantation, which includes most of the re-infusions that were performed, about 60% of all recipients experienced a reportable adverse event (Exhibit 7-2), with a decline in the most recent era (p=0.02). About one-third have experienced a serious adverse event within the first year, with a significant decline in the most recent era. This pattern is also seen for all adverse events in all follow-up after islet transplantation (Exhibit 7-3).

The outcomes of the reported adverse events have improved over the decade, with fewer patients experiencing long-term sequelae of their adverse events in the most recent era (Exhibit 7-4).

Many adverse events seen in this population are unrelated to islet transplantation but not unexpected in a cohort of older T1D with significant co-morbidity.

Overall, 13% of all recipients failed to recover completely from an adverse event (Exhibit 7-5). There have been 18 or 1.3% deaths, with 15 in the early cohort 1999-2003 (Exhibit 7-11), although cumulative mortality rates by era are not different.

Expressed as events per person-year of follow-up, both non-serious and serious reportable adverse events occur with a frequency of about 0.1 event per person-year, with a concentration in the first year of 0.5-0.7 (Exhibit 7-7). AEs related to immunosupression (IS) are also most frequent in the first year of follow-up (Exhibits 7-7B and 7-8B) and then decline rapidly after the first year.

Exhibit 7-9 displays trends in AE and SAE incidence according to type of transplant, era and relatedness to the infusion procedure and immunosuppression. While marginally significant differences are noted by era (see above), there may be differences according to immunsouppression strategies and patient characteristics that deserve further investigation.

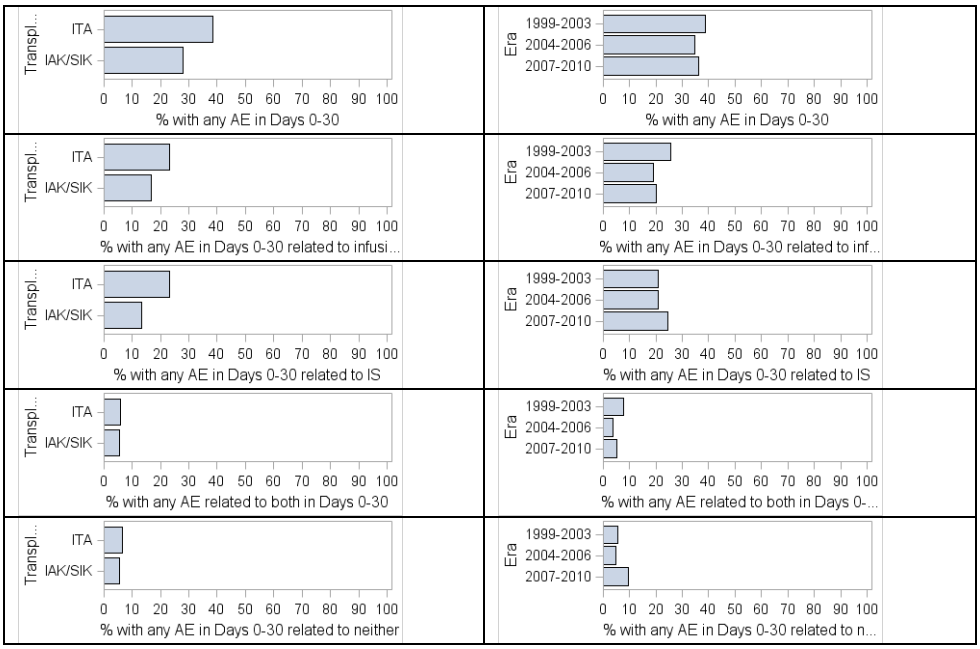
There have been 16 instances in 13 patients of basal or squamous carcinoma of the skin (Exhibit 7-10). There have been 12 recipients who developed non-skin cancers, of whom six (50%) recovered completely, 2 recovered with sequelae, 3 did not recover, and one died. In recent reports, malignancy may be increased with either diabetes or with the use of immunosuppression. It is difficult with these few cases to definitively determine if the reported neoplasms are related to islet transplantation.

Of the 18 reported deaths, three were deemed possibly related and one was deemed definitely related to islet transplantation or immunosuppression (Exhibit 7-11).

Life-threatening events have occurred in 26% of recipients in 1999-2003 and only 11% in 2007-2009 (p=0.02, Exhibit 7-12). Most involved neutropenia and abnormal liver function. The vast majority recovered, 4 died (included above), 7 did not recover, and 12 recovered with sequelae.

Exhibit 7-1A
Adverse Events (AEs) in Days 0-30 Post First Infusion

	Type				Era					
	ITA		IAK/SIK		1999-2003		2004-2006		2007-2010	
	N	%	N	%	N	%	N	%	N	%
Recipients with any AE in Days 0-30	185	38.5	25	27.8	95	38.6	66	34.7	49	36.3
Recipients with any AE related to infusion and IS in Days 0-30	28	5.8	5	5.6	19	7.7	7	3.7	7	5.2
Recipients with any AE related to infusion in Days 0-30	111	23.1	15	16.7	63	25.6	36	18.9	27	20.0
Recipients with any AE related to IS in Days 0-30	112	23.3	12	13.3	51	20.7	40	21.1	33	24.4
Recipients with any AE unrelated to infusion or IS in Days 0-30	31	6.4	5	5.6	14	5.7	9	4.7	13	9.6

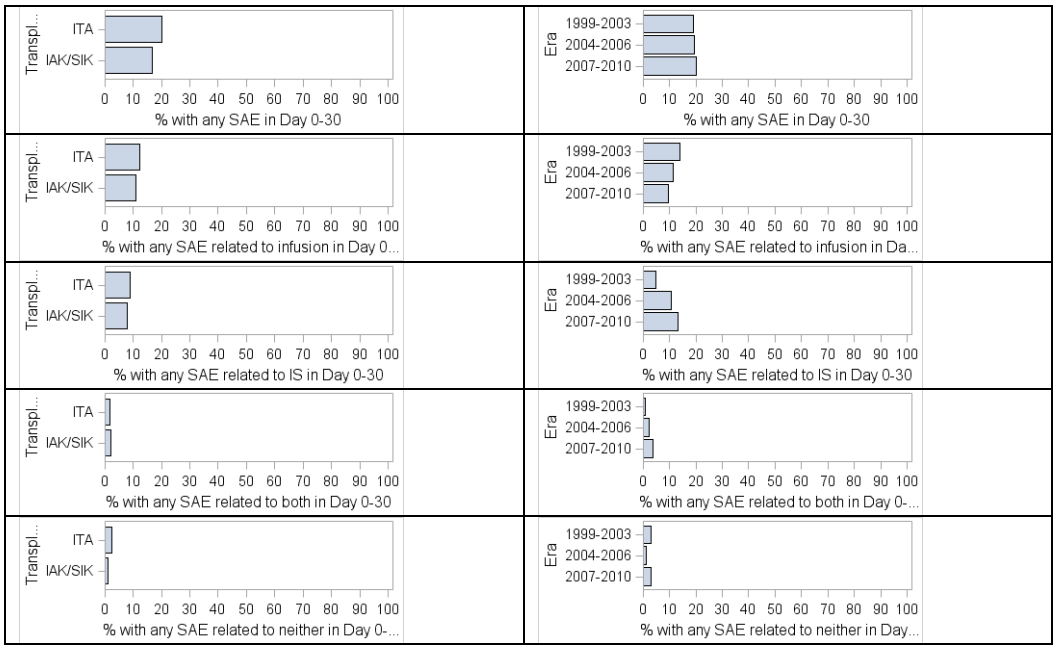


Frequency of AEs in Days 0-30 post first infusion (by Organ Class and Preferred Term)		Overall	Transplant type		Era		
			ITA	IAK/SIK	1999-2003	2004-2006	2007-2010
		N	N	N	N	N	N
System/Organ Class	**Preferred term**						
Blood and lymphatic system disorders	**Anaemia**	7	6	1	3	2	2
	Blood disorder	3	3	.	.	.	3
	Lymphopenia	21	20	1	1	8	12
	Platelet disorder	2	2	.	1	.	1
Cardiac disorders	**Arrhythmia supraventricular**	1	1	.	.	.	1
	Cardiac disorder	1	1	.	.	.	1
	Myocardial ischaemia	3	3	.	2	.	1

Frequency of AEs in Days 0-30 post first infusion (by Organ Class and Preferred Term)		Overall	Transplant type		Era		
			ITA	IAK/SIK	1999-2003	2004-2006	2007-2010
		N	N	N	N	N	N
Gastrointestinal disorders	Ascites	1	1	.	1	.	.
	Diarrhoea	5	4	1	1	3	1
	Gastrointestinal disorder	1	1	.	.	1	.
	Gastrointestinal haemorrhage	3	1	2	2	1	.
	Gastrointestinal obstruction	1	1	.	.	.	1
	Gastrointestinal perforation	1	1	.	.	.	1
	Haemorrhoids	1	1	.	1	.	.
	Ileus	1	1	.	1	.	.
	Nausea	4	3	1	2	1	1
	Peritoneal haemorrhage	18	13	5	10	3	5
	Vomiting	4	4	.	2	.	2
General disorders and administration site conditions	Mucosal inflammation	1	1	.	.	1	.
	Oedema peripheral	1	1	.	.	.	1
	Pain	8	8	.	2	3	3
	Pyrexia	1	1	.	.	1	.
Hepatobiliary disorders	Cholecystitis	3	2	1	1	.	2
	Portal vein thrombosis	5	5	.	3	2	.
Immune system disorders	Hypersensitivity	2	2	.	2	.	.
Infections and infestations	Infection	7	5	2	1	5	1
Injury, poisoning and procedural complications	Fracture	1	1	.	.	1	.
Investigations	Activated partial thromboplastin time	1	1	.	1	.	.
	Blood alkaline phosphatase	14	13	1	5	7	2
	Gamma-glutamyltransferase	6	5	1	2	2	2
	Granulocytes abnormal	98	97	1	43	33	22
	Lipase	4	1	3	2	2	.
	Liver function test abnormal	86	84	2	46	26	14
	Low density lipoprotein abnormal	1	1	.	.	.	1
	Troponin T	1	1	.	.	.	1
	Weight increased	1	1	.	.	.	1
Metabolism and nutrition disorders	Hyperkalaemia	1	1	.	1	.	.
	Hypoalbuminaemia	1	1	.	1	.	.
	Hypoglycaemia	14	14	.	5	6	3
	Hypokalaemia	3	3	.	.	1	2
	Hyponatraemia	2	1	1	.	1	1
	Hypophosphataemia	4	3	1	.	.	4
	Ketoacidosis	15	13	2	8	5	2
Musculoskeletal and connective tissue disorders	Muscular weakness	1	1	.	.	1	.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm malignant	1	1	.	1	.	.
Nervous system disorders	Cerebral ischaemia	1	1	.	1	.	.
	Dyskinesia	1	1	.	.	.	1
Respiratory, thoracic and mediastinal disorders	Aspiration	1	1	.	.	.	1
	Dyspnoea	2	2	.	1	.	1
	Haemothorax	1	.	1	1	.	.
	Hypoxia	4	4	.	.	.	4
	Lung disorder	1	.	1	.	1	.
	Pneumonitis	1	.	1	1	.	.
	Pulmonary hypertension	1	1	.	.	.	1
Skin and subcutaneous tissue disorders	Exfoliative rash	2	2	.	.	.	2
Surgical and medical procedures	Surgery	1	1	.	1	.	.
Vascular disorders	Haematoma	4	3	1	1	2	1
	Haemorrhage	4	3	1	1	2	1
	Hypertension	1	.	1	.	1	.
	Hypotension	2	2	.	.	.	2
	Thrombosis	2	2	.	2	.	.

Exhibit 7-1B
Serious Adverse Events (SAEs) in Days 0-30 Post First Infusion

Percent of Recipients with:	Type				Era					
	ITA		IAK/SIK		1999-2003		2004-2006		2007-2010	
	N	%	N	%	N	%	N	%	N	%
Any SAE in Days 0-30	96	20.0	15	16.7	47	19.1	37	19.5	27	20.0
Any SAE in Days 0-30 related to infusion	59	12.3	10	11.1	34	13.8	22	11.6	13	9.6
Any SAE in Days 0-30 related to IS	43	8.9	7	7.8	12	4.9	20	10.5	18	13.3
Any SAE in Days 0-30 related to infusion and IS	9	1.9	2	2.2	2	0.8	4	2.1	5	3.7
Any SAE in Days 0-30 unrelated to infusion or IS	12	2.5	1	1.1	7	2.8	2	1.1	4	3.0



SAEs in Days 0-30 by System/Organ Class and Preferred Term		Overall	Transplant type		Era		
			ITA	IAK/SIK	1999-2003	2004-2006	2007-2010
		N	N	N	N	N	N
System/Organ Class	**Preferred term**						
Blood and lymphatic system disorders	**Anaemia**	7	6	1	3	2	2
	Blood disorder	3	3	.	.	.	3
	Lymphopenia	21	20	1	1	8	12
	Platelet disorder	2	2	.	1	.	1
Cardiac disorders	**Arrhythmia supraventricular**	1	1	.	.	.	1
	Cardiac disorder	1	1	.	.	.	1
	Myocardial ischaemia	3	3	.	2	.	1

SAEs in Days 0-30 by System/Organ Class and Preferred Term		Overall	Transplant type		Era		
			ITA	IAK/SIK	1999-2003	2004-2006	2007-2010
		N	N	N	N	N	N
Gastrointestinal disorders	Ascites	1	1	.	1	.	.
	Diarrhoea	5	4	1	1	3	1
	Gastrointestinal disorder	1	1	.	.	1	.
	Gastrointestinal haemorrhage	3	1	2	2	1	.
	Gastrointestinal obstruction	1	1	.	.	.	1
	Gastrointestinal perforation	1	1	.	.	.	1
	Haemorrhoids	1	1	.	1	.	.
	Ileus	1	1	.	1	.	.
	Nausea	4	3	1	2	1	1
	Peritoneal haemorrhage	18	13	5	10	3	5
	Vomiting	4	4	.	2	.	2
General disorders and administration site conditions	Mucosal inflammation	1	1	.	.	1	.
	Oedema peripheral	1	1	.	.	.	1
	Pain	8	8	.	2	3	3
	Pyrexia	1	1	.	.	1	.
Hepatobiliary disorders	Cholecystitis	3	2	1	1	.	2
	Portal vein thrombosis	5	5	.	3	2	.
Immune system disorders	Hypersensitivity	2	2	.	2	.	.
Infections and infestations	Infection	7	5	2	1	5	1
Injury, poisoning and procedural complications	Fracture	1	1	.	.	1	.
Investigations	Activated partial thromboplastin time	1	1	.	1	.	.
	Blood alkaline phosphatase	14	13	1	5	7	2
	Gamma-glutamyltransferase	6	5	1	2	2	2
	Granulocytes abnormal	98	97	1	43	33	22
	Lipase	4	1	3	2	2	.
	Liver function test abnormal	86	84	2	46	26	14
	Low density lipoprotein abnormal	1	1	.	.	.	1
	Troponin T	1	1	.	.	.	1
	Weight increased	1	1	.	.	.	1
Metabolism and nutrition disorders	Hyperkalaemia	1	1	.	1	.	.
	Hypoalbuminaemia	1	1	.	1	.	.
	Hypoglycaemia	14	14	.	5	6	3
	Hypokalaemia	3	3	.	.	1	2
	Hyponatraemia	2	1	1	.	1	1
	Hypophosphataemia	4	3	1	.	.	4
	Ketoacidosis	15	13	2	8	5	2
Musculoskeletal and connective tissue disorders	Muscular weakness	1	1	.	.	1	.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm malignant	1	1	.	1	.	.
Nervous system disorders	Cerebral ischaemia	1	1	.	1	.	.
	Dyskinesia	1	1	.	.	.	1
Respiratory, thoracic and mediastinal disorders	Aspiration	1	1	.	.	.	1
	Dyspnoea	2	2	.	1	.	1
	Haemothorax	1	.	1	1	.	.
	Hypoxia	4	4	.	.	.	4
	Lung disorder	1	.	1	.	1	.
	Pneumonitis	1	.	1	1	.	.
	Pulmonary hypertension	1	1	.	.	.	1
Skin and subcutaneous tissue disorders	Exfoliative rash	2	2	.	.	.	2
Surgical and medical procedures	Surgery	1	1	.	1	.	.

SAEs in Days 0-30 by System/Organ Class and Preferred Term		Overall	Transplant type		Era		
			ITA	IAK/SIK	1999-2003	2004-2006	2007-2010
		N	N	N	N	N	N
Vascular disorders	**Haematoma**	4	3	1	1	2	1
	Haemorrhage	4	3	1	1	2	1
	Hypertension	1	.	1	.	1	.
	Hypotension	2	2	.	.	.	2
	Thrombosis	2	2	.	2	.	.

Exhibit 7-2A
Adverse Event (AEs) in Year 1 Post First Infusion

	Type				Era					
	ITA		IAK/SIK		1999-2003		2004-2006		2007-2010	
	N	%	N	%	N	%	N	%	N	%
Recipients with any adverse event in year 1	281	58.4	51	56.7	184	59.9	99	60.4	49	49.0
Recipients with any AE related to infusion AND immunosuppression in Year 1	53	11.0	7	7.8	37	12.1	16	9.8	7	7.0
Recipients with any AE related to infusion in Year 1	160	33.3	27	30.0	107	34.9	54	32.9	26	26.0
Recipient with any AE related to immunosuppression in Year 1	204	42.4	31	34.4	127	41.4	73	44.5	35	35.0
Recipients with any AE unrelated to infusion or immunosuppression in Year 1	86	17.9	15	16.7	56	18.2	24	14.6	21	21.0

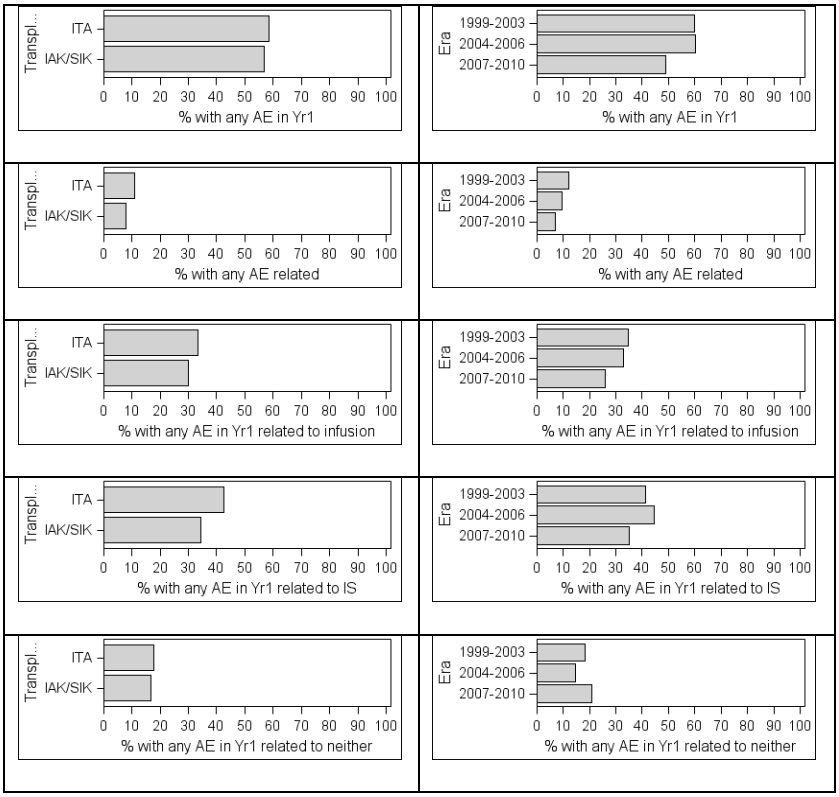


Exhibit 7-2B
Recipients with a Serious Adverse Event (SAE) in Year 1 Post First Infusion

	Type				Era					
	ITA		IAK/SIK		1999-2003		2004-2006		2007-2010	
	N	%	N	%	N	%	N	%	N	%
Recipients with any SAE in Year 1	189	39.3	39	43.3	126	41.0	69	42.1	33	33.0
Recipients with any SAE related to infusion AND immunosuppression in Year 1	23	4.8	2	2.2	10	3.3	10	6.1	5	5.0
Recipients with any SAE related to infusion in Year 1	100	20.8	18	20.0	66	21.5	37	22.6	15	15.0
Recipients with any SAE related to immunosuppression in Year 1	117	24.3	23	25.6	73	23.8	45	27.4	22	22.0
Recipients with any SAE unrelated to infusion or immunosuppression in Year 1	41	8.5	11	12.2	29	9.4	16	9.8	7	7.0

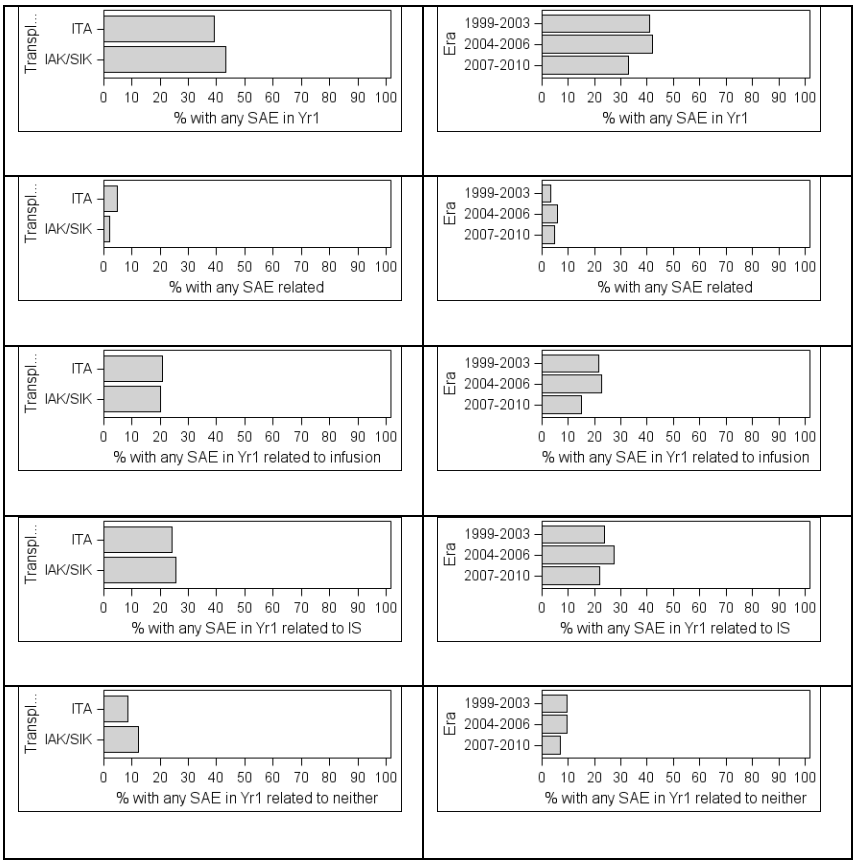


Exhibit 7-3A
Recipients with an Adverse Event (AE) any time post islet transplantation

	Type				Era					
	ITA		IAK/SIK		1999-2003		2004-2006		2007-2010	
	N	%	N	%	N	%	N	%	N	%
Any AE ever post islet transplant	324	67.4	59	65.6	217	70.7	115	70.1	51	51.0
Any AE ever related to infusion and IS	65	13.5	7	7.8	39	12.7	23	14.0	10	10.0
Any AE ever related to infusion	179	37.2	33	36.7	122	39.7	63	38.4	27	27.0
Any AE ever related to IS	247	51.4	40	44.4	159	51.8	88	53.7	40	40.0
Any AE ever unrelated to infusion or IS	140	29.1	28	31.1	96	31.3	47	28.7	25	25.0

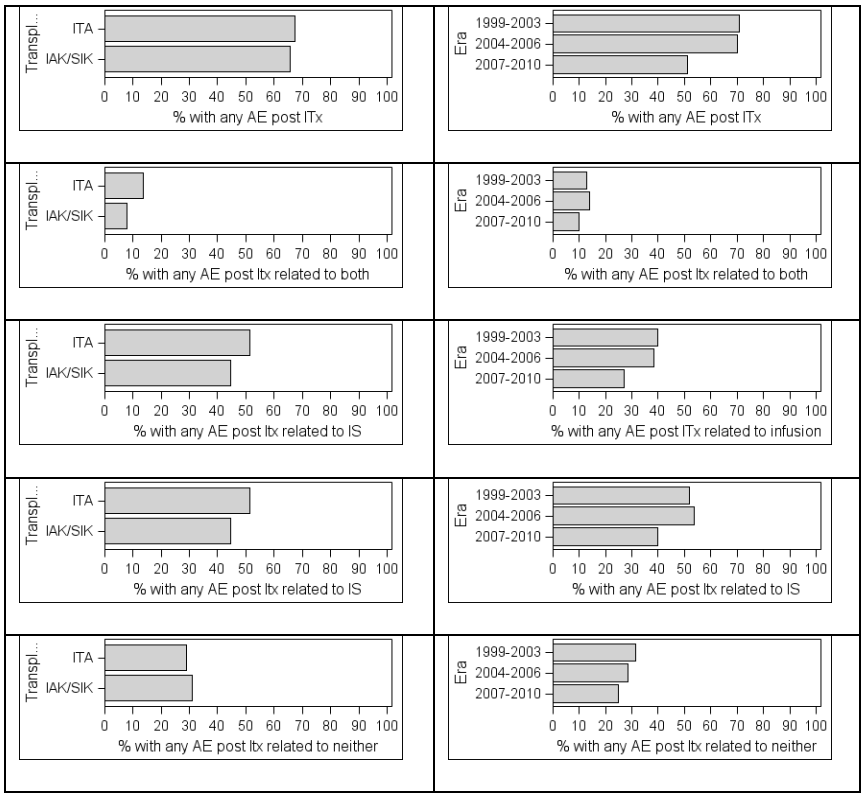


Exhibit 7-3B
Recipients with a Serious Adverse Event (SAE) any time post islet transplantation

	Type				Era					
	ITA		IAK/SIK		1999-2003		2004-2006		2007-2009	
	N	%	N	%	N	%	N	%	N	%
Any SAE ever post islet transplant	244	50.7	50	55.6	169	55.0	90	54.9	35	35.0
Any SAE ever related to infusion and IS	33	6.9	2	2.2	11	3.6	16	9.8	8	8.0
Any SAE ever related to infusion	118	24.5	21	23.3	77	25.1	45	27.4	17	17.0
Any SAE ever related to IS	162	33.7	36	40.0	108	35.2	64	39.0	26	26.0
Any SAE ever unrelated to infusion or IS	90	18.7	25	27.8	68	22.1	36	22.0	11	11.0

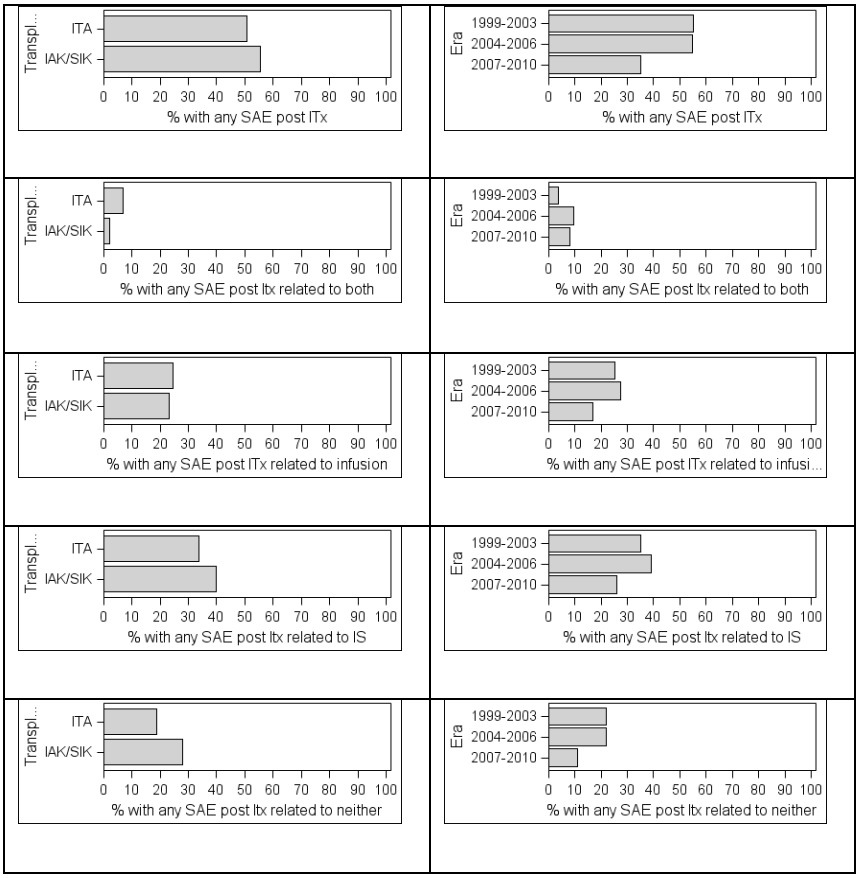
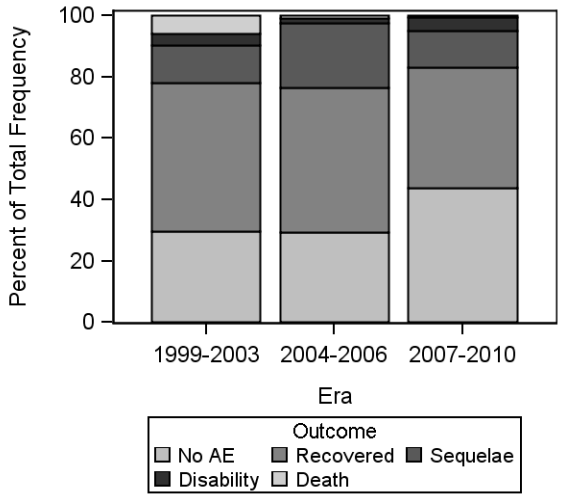


Exhibit 7-4
Worst Outcome of Any Adverse Events per Recipient

	Total		Transplant type				Era					
	Total		ITA		IAK/SIK		1999-2003		2004-2006		2007-2010	
	N	%	N	%	N	%	N	%	N	%	N	%
Total	571	100.0	481	100.0	90	100.0	246	100.0	190	100.0	135	100.0
No AE	188	32.9	157	32.6	31	34.4	73	29.7	56	29.5	59	43.7
Recovered	261	45.7	224	46.6	37	41.1	119	48.4	89	46.8	53	39.3
Sequelae	86	15.1	72	15.0	14	15.6	30	12.2	40	21.1	16	11.9
Disability	18	3.2	16	3.3	2	2.2	9	3.7	3	1.6	6	4.4
Death	18	3.2	12	2.5	6	6.7	15	6.1	2	1.1	1	0.7



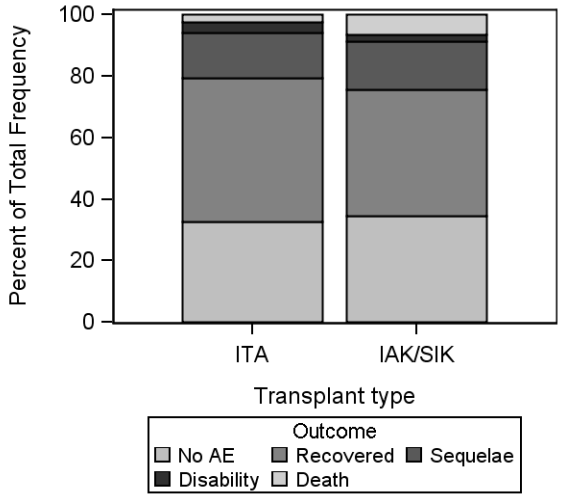


Exhibit 7-5
All Adverse Events Following Islet Transplant in order by frequency, with final outcome

	Outcome					
	Total	0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
	N	Row %	Row %	Row %	Row %	Row %
Total adverse events following islet transplantation	**1,415**	0.7	85.1	11.4	1.6	1.3

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
Order by frequency	**Adverse event**						
1	**Granulocytes abnormal**	256	.	95.3	4.3	0.4	.
2	**Liver function test abnormal**	227	50.2	48.0	1.8	.	.
3	**Ketoacidosis**	110	.	96.4	3.6	.	.
4	**Infection**	98	.	83.7	14.3	.	2.0
5	**Hypoglycaemia**	76	.	94.7	3.9	1.3	.
6	**Pain**	79	.	83.5	16.5	.	.
7	**Peritoneal haemorrhage**	44	.	97.7	2.3	.	.
8	**Diarrhoea**	54	.	77.8	20.4	1.9	.
9	**Lymphopenia**	73	50.7	45.2	4.1	.	.
10	**Anaemia**	33	.	100.0	.	.	.
11	**Neoplasm malignant**	49	51.0	30.6	16.3	2.0	.
12	**Blood alkaline phosphatase**	23	.	91.3	8.7	.	.
13	**Gastrointestinal disorder**	22	.	95.5	4.5	.	.
14	**Vomiting**	21	.	90.5	4.8	4.8	.
15	**Hypersensitivity**	34	52.9	20.6	23.5	.	2.9
16	**Mucosal inflammation**	19	.	84.2	10.5	5.3	.
17	**Hypertension**	19	.	73.7	26.3	.	.
18	**Renal failure**	19	.	73.7	21.1	5.3	.
19	**Fatigue**	14	.	92.9	.	7.1	.
20	**Cholecystitis**	13	.	92.3	.	7.7	.
21	**Fracture**	17	.	70.6	29.4	.	.
22	**Gamma-glutamyltransferase**	15	.	80.0	20.0	.	.
23	**Hyponatraemia**	14	.	85.7	14.3	.	.
24	**Hypophosphataemia**	11	.	100.0	.	.	.
25	**Myocardial ischaemia**	21	52.4	23.8	19.0	4.8	.
26	**Wound complication**	11	.	100.0	.	.	.
27	**Eye disorder**	13	.	76.9	7.7	15.4	.
28	**Gastrointestinal obstruction**	14	.	71.4	28.6	.	.
29	**Hypokalaemia**	11	.	90.9	.	9.1	.
30	**Portal vein thrombosis**	12	.	83.3	8.3	8.3	.
31	**Death (no other information)**	9	.	.	.	.	100.0
32	**Haematoma**	10	.	90.0	10.0	.	.

Exhibit 7-5 (continued)
All Adverse Events Following Islet Transplant in order by frequency, with final outcome

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
33	Haemorrhage	11	.	81.8	9.1	.	9.1
34	Hyperkalaemia	10	.	90.0	10.0	.	.
35	Sexual dysfunction	10	.	90.0	10.0	.	.
36	Muscular weakness	15	53.3	33.3	13.3	.	.
37	Blood disorder	7	.	100.0	.	.	.
38	Cerebral ischaemia	13	53.8	7.7	23.1	7.7	7.7
39	Colitis	9	.	77.8	22.2	.	.
40	Dehydration	7	.	100.0	.	.	.
41	Nausea	8	.	87.5	12.5	.	.
42	Surgery	10	.	70.0	10.0	20.0	.
43	Exfoliative rash	7	.	85.7	14.3	.	.
44	Hypoxia	6	.	100.0	.	.	.
45	Lung disorder	7	.	85.7	14.3	.	.
46	Pneumonitis	7	.	85.7	.	.	14.3
47	Pyrexia	6	.	100.0	.	.	.
48	Ascites	5	.	100.0	.	.	.
49	Gastrointestinal haemorrhage	5	.	100.0	.	.	.
50	Lipase	5	.	100.0	.	.	.
51	Musculoskeletal disorder	7	.	71.4	14.3	14.3	.
52	Oedema peripheral	5	.	100.0	.	.	.
53	Proteinuria	9	.	55.6	44.4	.	.
54	Syncope	5	.	100.0	.	.	.
55	Urinary bladder haemorrhage	6	.	83.3	16.7	.	.
56	Dyspnoea	5	.	80.0	20.0	.	.
57	Mood altered	5	.	.	80.0	20.0	.
58	Peripheral ischaemia	6	.	66.7	33.3	.	.
59	Platelet disorder	4	.	100.0	.	.	.
60	Renal disorder	4	.	100.0	.	.	.
61	Thrombosis	5	.	80.0	20.0	.	.
62	Albuminuria	5	.	60.0	40.0	.	.
63	Dizziness	3	.	100.0	.	.	.
64	Hypoalbuminaemia	3	.	100.0	.	.	.
65	Pulmonary hypertension	5	60.0	20.0	20.0	.	.
66	Skin disorder	5	60.0	40.0	.	.	.
67	Tremor	3	.	100.0	.	.	.
68	Activated partial thromboplastin time	2	.	100.0	.	.	.
69	Acute respiratory distress syndrome	2	.	.	.	.	100.0
70	Arrhythmia supraventricular	2	.	100.0	.	.	.
71	Arthritis	2	.	.	.	100.0	.
72	Aspiration	2	.	100.0	.	.	.

Exhibit 7-5 (continued)
All Adverse Events Following Islet Transplant in order by frequency, with final outcome

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
73	Biliary tract disorder	2	.	100.0	.	.	.
74	Blood amylase	2	.	100.0	.	.	.
75	Cardiac disorder	2	.	100.0	.	.	.
76	Confusional state	2	.	100.0	.	.	.
77	Constipation	3	.	66.7	.	33.3	.
78	Decubitus ulcer	2	.	.	100.0	.	.
79	Gastrointestinal perforation	2	.	100.0	.	.	.
80	Glomerular filtration rate	3	.	66.7	33.3	.	.
81	Haemothorax	2	.	100.0	.	.	.
82	Hypotension	2	.	100.0	.	.	.
83	Ileus	2	.	100.0	.	.	.
84	Insomnia	3	.	66.7	33.3	.	.
85	Low density lipoprotein abnormal	3	.	66.7	33.3	.	.
86	Menstruation irregular	3	.	66.7	33.3	.	.
87	Myocarditis	2	.	100.0	.	.	.
88	Opportunistic infection	2	.	100.0	.	.	.
89	Pericardial effusion	2	.	100.0	.	.	.
90	Pleural effusion	2	.	100.0	.	.	.
91	Retinal detachment	2	.	100.0	.	.	.
92	Ulcer	2	.	100.0	.	.	.
93	Vitreous haemorrhage	2	.	.	100.0	.	.
94	Weight decreased	2	.	100.0	.	.	.
95	Arthropathy	1	.	100.0	.	.	.
96	Ataxia	1	.	100.0	.	.	.
97	Blood bilirubin	1	.	100.0	.	.	.
98	Blood creatine phosphokinase	1	.	100.0	.	.	.
99	Cardio-respiratory arrest	1	.	.	.	.	100.0
100	Cough	1	.	100.0	.	.	.
101	Decreased appetite	1	.	100.0	.	.	.
102	Dyskinesia	1	.	100.0	.	.	.
103	Dysphagia	1	.	.	100.0	.	.
104	Ear infection	1	.	.	100.0	.	.
105	Endocrine disorder	1	.	100.0	.	.	.
106	Enteritis	1	.	100.0	.	.	.
107	Febrile neutropenia	1	.	100.0	.	.	.
108	Haemoglobinuria	1	.	100.0	.	.	.
109	Haemolysis	1	.	100.0	.	.	.
110	Haemorrhoids	1	.	100.0	.	.	.
111	Hearing impaired	1	.	.	100.0	.	.
112	Hypocalcaemia	1	.	100.0	.	.	.
113	Hypomagnesaemia	1	.	100.0	.	.	.
114	Injection site reaction	1	.	100.0	.	.	.
115	Injury	1	.	.	100.0	.	.

Exhibit 7-5 (continued)
All Adverse Events Following Islet Transplant in order by frequency, with final outcome

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
116	**Myositis**	1	.	100.0	.	.	.
117	**Ocular surface disease**	1	.	100.0	.	.	.
118	**Pancreatitis**	1	.	100.0	.	.	.
119	**Pericarditis**	1	.	100.0	.	.	.
120	**Presyncope**	1	.	100.0	.	.	.
121	**Pruritus**	1	.	.	100.0	.	.
122	**Psychotic disorder**	1	.	100.0	.	.	.
123	**Soft tissue necrosis**	1	.	.	100.0	.	.
124	**Tinnitus**	1	.	.	100.0	.	.
125	**Troponin I**	1	.	100.0	.	.	.
126	**Troponin T**	1	.	100.0	.	.	.
127	**Weight increased**	1	.	100.0	.	.	.

Exhibit 7-6
SAE Criteria

	Transplant type				Era					
	ITA		IAK/SIK		1999-2003		2004-2006		2007-2010	
	N	%	N	%	N	%	N	%	N	%
Total recipients (N)	481	100.0	90	100.0	246	100.0	190	100.0	135	100.0
Death	12	2.5	6	6.7	15	6.1	2	1.1	1	0.7
Life Threatening	109	22.7	23	25.6	64	26.0	54	28.4	14	10.4
Hospitilization	206	42.8	50	55.6	121	49.2	86	45.3	49	36.3
Long term disability	16	3.3	2	2.2	9	3.7	3	1.6	6	4.4
PI Indicated Serious	62	12.9	15	16.7	23	9.3	31	16.3	23	17.0

Exhibit 7-7A
ITA: Incidence of Post-Transplant AEs Related to Infusion Procedure

By calendar year

Study Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1999	7.8	1	0.13	0.00 - 0.71	1	0.13	0.00 - 0.71
2000	29.8	7	0.23	0.09 - 0.48	4	0.13	0.04 - 0.34
2001	62.6	14	0.22	0.12 - 0.38	5	0.08	0.03 - 0.19
2002	124.3	60	0.48	0.37 - 0.62	33	0.27	0.18 - 0.37
2003	191.3	50	0.26	0.19 - 0.34	26	0.14	0.09 - 0.20
2004	230.0	28	0.12	0.08 - 0.18	13	0.06	0.03 - 0.10
2005	289.1	49	0.17	0.13 - 0.22	30	0.10	0.07 - 0.15
2006	339.9	26	0.08	0.05 - 0.11	21	0.06	0.04 - 0.09
2007	367.7	16	0.04	0.02 - 0.07	10	0.03	0.01 - 0.05
2008	397.5	21	0.05	0.03 - 0.08	12	0.03	0.02 - 0.05
2009	445.0	22	-	0.03 - 0.07	10	-	0.01 - 0.04

By year of follow-up post first infusion

Recipient Follow-Up Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1	441.8	259	0.59	0.52 - 0.66	142	0.32	0.27 - 0.38
2	411.6	20	0.05	0.03 - 0.08	15	0.04	0.02 - 0.06
3	353.4	10	0.03	0.01 - 0.05	5	0.01	0.00 - 0.03
4	318.3	9	0.03	0.01 - 0.05	7	0.02	0.01 - 0.05
5	273.6	4	0.01	0.00 - 0.04	3	0.01	0.00 - 0.03
6	252.3	1	0.00	0.00 - 0.02	1	0.00	0.00 - 0.02
7	216.6	0	0.00	0.00 - 0.02	0	0.00	0.00 - 0.02
8	195.1	0	0.00	0.00 - 0.02	0	0.00	0.00 - 0.02
9	160.7	0	0.00	0.00 - 0.02	0	0.00	0.00 - 0.02
10	136.9	0	0.00	0.00 - 0.03	0	0.00	0.00 - 0.03

In ITA, the incidence of infusion-related adverse events and serious adverse events dropped to less than 0.1 events/person-year in 2006-2009, relative to 0.08-0.27 in 1999-2005 ($p<0.05$). The vast majority occurred in the first year post islet transplant, which included most re-infusions.

Exhibit 7-7B
ITA: Incidence of Post-Transplant AEs Related to Immunosuppression Therapy

By calendar year

Study Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1999	7.8	5	0.64	0.21 - 1.50	5	0.64	0.21 - 1.50
2000	29.8	8	0.27	0.12 - 0.53	3	0.10	0.02 - 0.29
2001	62.6	16	0.26	0.15 - 0.42	2	0.03	0.00 - 0.12
2002	124.3	93	0.75	0.60 - 0.92	33	0.27	0.18 - 0.37
2003	191.3	85	0.44	0.35 - 0.55	27	0.14	0.09 - 0.21
2004	230.0	85	0.37	0.30 - 0.46	28	0.12	0.08 - 0.18
2005	289.1	142	0.49	0.41 - 0.58	65	0.22	0.17 - 0.29
2006	339.9	73	0.21	0.17 - 0.27	33	0.10	0.07 - 0.14
2007	367.7	39	0.11	0.08 - 0.14	27	0.07	0.05 - 0.11
2008	397.5	57	0.14	0.11 - 0.19	31	0.08	0.05 - 0.11
2009	445.0	60	-	0.10 - 0.17	24	-	0.03 - 0.08

By follow-up year

Recipient Follow-Up Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1	441.8	472	1.07	0.97 - 1.17	178	0.40	0.35 - 0.47
2	411.6	100	0.24	0.20 - 0.30	39	0.09	0.07 - 0.13
3	353.4	45	0.13	0.09 - 0.17	30	0.08	0.06 - 0.12
4	318.3	28	0.09	0.06 - 0.13	22	0.07	0.04 - 0.10
5	273.6	17	0.06	0.04 - 0.10	11	0.04	0.02 - 0.07
6	252.3	9	0.04	0.02 - 0.07	6	0.02	0.01 - 0.05
7	216.6	3	0.01	0.00 - 0.04	2	0.01	0.00 - 0.03
8	195.1	3	0.02	0.00 - 0.04	2	0.01	0.00 - 0.04
9	160.7	1	0.01	0.00 - 0.03	1	0.01	0.00 - 0.03
10	136.9	0	0.00	0.00 - 0.03	0	0.00	0.00 - 0.03

In ITA recipients, the incidence of immunosuppression-related adverse events and serious adverse events declined steadily over the decade, after a slight rise in 2002. The incidence was highest in the first year post first infusion.

Exhibit 7-8A
IAK/SIK: Incidence of Post-Transplant AEs Related to Infusion Procedure

By calendar year

Study Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1999	2.6	1	0.38	0.01 - 2.14	1	0.38	0.01 - 2.14
2000	6.9	0	0.00	0.00 - 0.53	0	0.00	0.00 - 0.53
2001	10.3	4	0.39	0.11 - 0.99	2	0.19	0.02 - 0.70
2002	15.9	3	0.19	0.04 - 0.55	0	0.00	0.00 - 0.23
2003	26.8	9	0.34	0.15 - 0.64	7	0.26	0.11 - 0.54
2004	40.8	5	0.12	0.04 - 0.29	2	0.05	0.01 - 0.18
2005	52.4	8	0.15	0.07 - 0.30	2	0.04	0.00 - 0.14
2006	64.3	6	0.09	0.03 - 0.20	3	0.05	0.01 - 0.14
2007	73.8	3	0.04	0.01 - 0.12	3	0.04	0.01 - 0.12
2008	80.1	2	0.02	0.00 - 0.09	2	0.02	0.00 - 0.09
2009	83.4	1	-	0.00 - 0.07	1	-	0.00 - 0.07

By Follow-up year

Recipient Follow-Up Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1	87.4	34	0.39	0.27 - 0.54	19	0.22	0.13 - 0.34
2	83.4	2	0.02	0.00 - 0.09	1	0.01	0.00 - 0.07
3	74.0	3	0.04	0.01 - 0.12	0	0.00	0.00 - 0.05
4	73.0	1	0.01	0.00 - 0.08	1	0.01	0.00 - 0.08
5	69.7	2	0.03	0.00 - 0.10	2	0.03	0.00 - 0.10
6	62.9	0	0.00	0.00 - 0.06	0	0.00	0.00 - 0.06
7	48.4	0	0.00	0.00 - 0.08	0	0.00	0.00 - 0.08
8	40.4	0	0.00	0.00 - 0.09	0	0.00	0.00 - 0.09
9	34.6	0	0.00	0.00 - 0.11	0	0.00	0.00 - 0.11
10	29.9	0	0.00	0.00 - 0.12	0	0.00	0.00 - 0.12

Exhibit 7-8B
IAK/SIK: Incidence of Post-Transplant AEs related to Immunosuppression Therapy

By calendar year

Study Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1999	2.6	0	0.00	0.00 - 1.42	0	0.00	0.00 - 1.42
2000	6.9	1	0.14	0.00 - 0.81	1	0.14	0.00 - 0.81
2001	10.3	5	0.49	0.16 - 1.13	4	0.39	0.11 - 0.99
2002	15.9	6	0.38	0.14 - 0.82	2	0.13	0.02 - 0.45
2003	26.8	7	0.26	0.11 - 0.54	5	0.19	0.06 - 0.44
2004	40.8	22	0.54	0.34 - 0.82	17	0.42	0.24 - 0.67
2005	52.4	14	0.27	0.15 - 0.45	9	0.17	0.08 - 0.33
2006	64.3	16	0.25	0.14 - 0.40	11	0.17	0.09 - 0.31
2007	73.8	7	0.09	0.04 - 0.20	7	0.09	0.04 - 0.20
2008	80.1	4	0.05	0.01 - 0.13	3	0.04	0.01 - 0.11
2009	83.4	4	-	0.01 - 0.12	3	-	0.01 - 0.11

By follow-up year

Recipient Follow-Up Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1	87.4	45	0.51	0.38 - 0.69	30	0.34	0.23 - 0.49
2	83.4	17	0.20	0.12 - 0.33	15	0.18	0.10 - 0.30
3	74.0	15	0.20	0.11 - 0.33	11	0.15	0.07 - 0.27
4	73.0	4	0.05	0.01 - 0.14	3	0.04	0.01 - 0.12
5	69.7	3	0.04	0.01 - 0.13	3	0.04	0.01 - 0.13
6	62.9	1	0.02	0.00 - 0.09	0	0.00	0.00 - 0.06
7	48.4	2	0.04	0.01 - 0.15	2	0.04	0.01 - 0.15
8	40.4	0	0.00	0.00 - 0.09	0	0.00	0.00 - 0.09
9	34.6	0	0.00	0.00 - 0.11	0	0.00	0.00 - 0.11
10	29.9	0	0.00	0.00 - 0.12	0	0.00	0.00 - 0.12

Exhibit 7-9
Incidence of AEs and SAEs per Recipient by Type of Transplant and Era

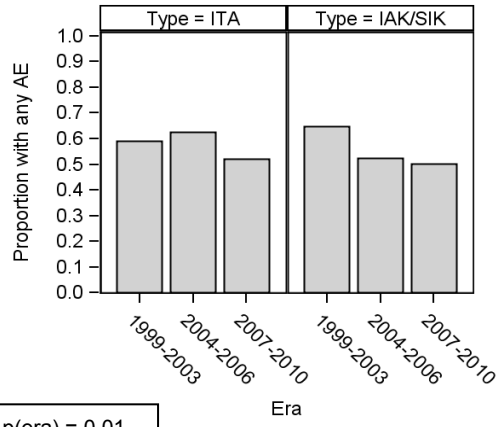
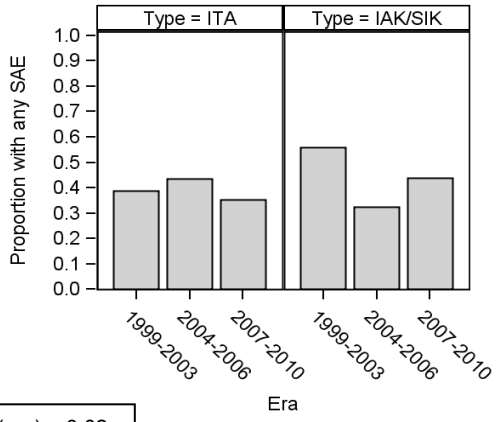
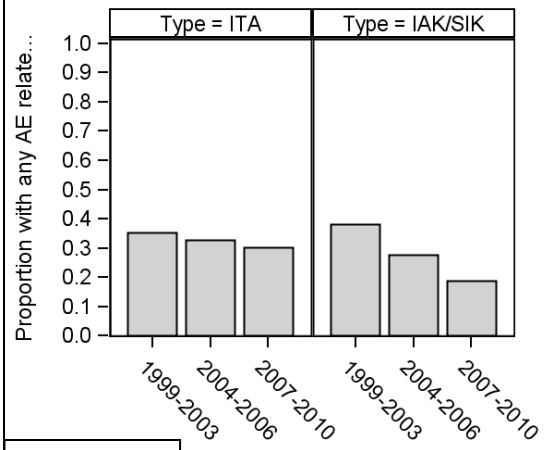
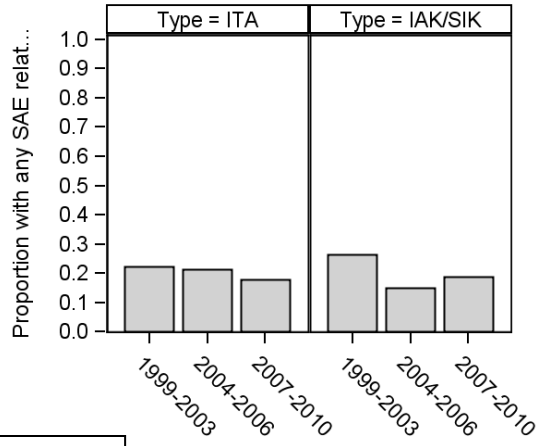
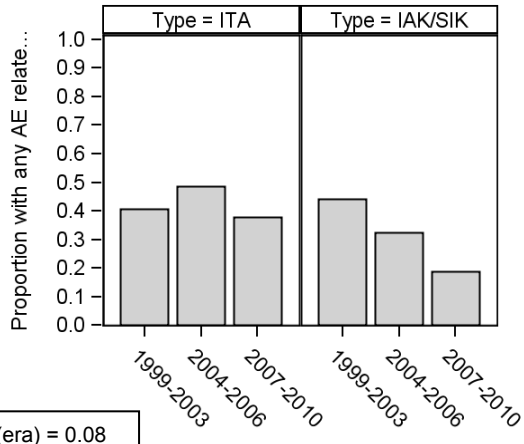
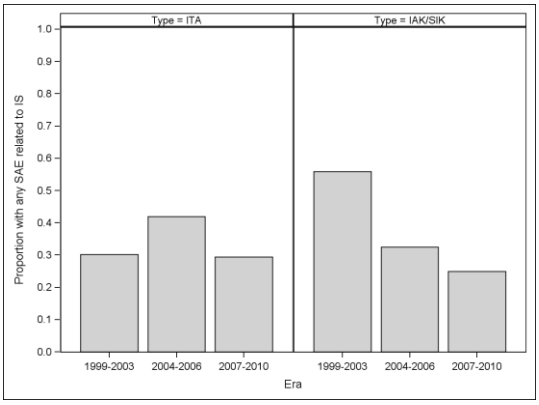
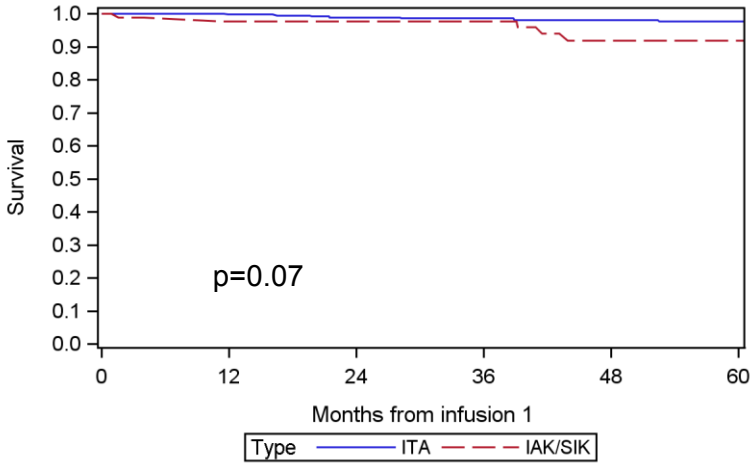
	Any AE	Any SAE
Proportion with any AE in First Year post Transplants	 p(era) = 0.01 p (type) = NS	 p(era) = 0.02 p (type) = NS
Proportion with any AE in First Year post Transplant Related to Infusion	 p(era) = 0.05 p (type) = NS	 p(era) = 0.14 p (type) = NS
Proportion with any AE in First Year post Transplants Related to Immuno-suppression	 p(era) = 0.08 p (type) = NS	 p(era) = NS p (type) = NS

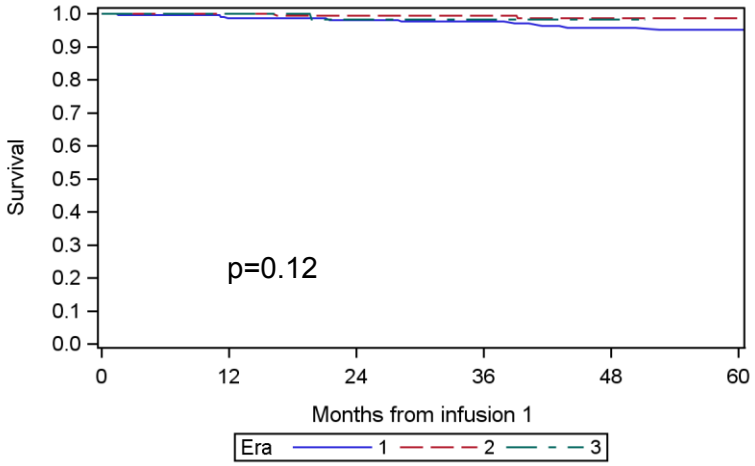
Exhibit 7-10
Summary of neoplasms reported post islet transplantation
CITR data as of 3/21/2011

Total recipients of Allo-ITx with first infusion as of 12/31/2009	**N=571 (481 ITA; 90 IAK/SIK)**
Mean follow-up / recipient	**3.2 (0-11.1) yrs**
Total person-years follow-up	**1,827 years**
Post-ITx incidence of cancer	**29 instances / 27 recipients (2 instances each in 2 recipients)**
Incidence rate	**0.02 events / person-year of follow-up**
Related to immunosuppression	**21 (72%) "possibly related" 8 (28%) not related**
By type	There were 16 instances in 13 patients (1 in 11 patients, 2 in one patient, and 3 in another) of basal or squamous cell carcinoma of the skin. The 11 patients with a single instance recovered completely, and the other two recovered with sequelae. There were 6 instances of malignant ovarian cysts, three instances of breast cancer (once in one patient and twice in another); two instances of lung cancer; and two instances of thyroid cancer. Of these 12 patients developing non-skin cancers, six (50%) recovered completely, 2 recovered with sequelae, 3 did not recover, and 1 died (lung).

Exhibit 7-11
Deaths



	ITA	IAK/SIK
Deaths/N	12/481 (2.5%)	6/90 (6.7%)



	1999-2003	2004-2006	2007-2009
Deaths/N	15/246 (6.1%)	2/190 (1.1)	1/135 (0.7%)

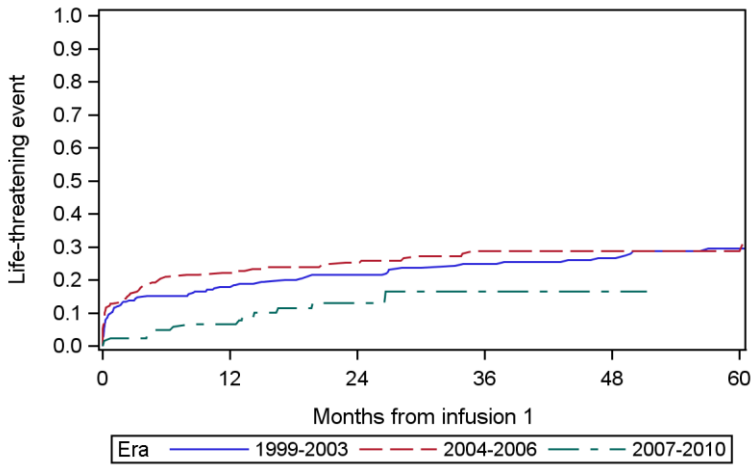
Exhibit 7-11 (Continued)
Deaths

PROJID	Type of Transplant	Years post infusion 1	Year of Transplant	MedDRA Primary Cause of Death	Related to Infusion Procedure?	Related to Immunosuppression Therapy?	Active Immunosupression
1	ITA	1	2000	Unknown	Not related	Unlikely related	Yes
2	ITA	1.4	2005	Cardiovascular-Atherosclerotic coronary artery Disease	Not related	Not related	Yes
3	ITA	1.7	2008	Multiorgan failure of unknown etiology	Possibly related	Possibly related	Yes
4	ITA	1.8	2003	Toxicity-Acute Methadone and Diphenhydramine	Not related	Not related	Yes
5	ITA	2.3	1999	Cardiovascular-Congestive heart failure	Not related	Not related	
6	ITA	3.2	2002	Infection-Viral meningitis	Not related	Possibly related	Yes
7	ITA	4.4	2001	Unknown	Not related	Unlikely related	Yes
8	ITA	5.3	2003	Infection-ARDS	Not related	Unlikely related	Yes
9	ITA	6.2	2000	Unknown	Not related	Unlikely related	Yes
10	ITA	6.5	2000	Diabetic ketoacidosis	Not related	Not related	Yes
11	ITA	8.2	2000	Infection-Pneumonia	Not related	Not related	Yes
12	ITA	8.8	1999	Cancer-Lung carcinoma non-small cell poorly differentiated	Not related	Unlikely related	Yes
13	IAK/SIK	0.1	2002	Infection-Infectious pneumopathy	Not related	Possibly related	Yes
14	IAK/SIK	0.9	2001	ARDS-Respiratory arrest after therapy withdrawal	Not related	Related	Yes
15	IAK/SIK	3.3	2004	Cerebrovascular-Brain hemorrhage	Not related	Not related	Yes
16	IAK/SIK	3.5	2001	Cerebrovascular- Massive hemorrhagic Infarct	Not related	Not related	Yes
17	IAK/SIK	3.7	2002	Cerebrovascular-Subarachnoid hemorrhage mesencephalic	Not related	Not related	Yes
18	IAK/SIK	6.3	2003	Infection-Pneumonia	Not related	Not related	Yes

There have been 18 reports of death to the Registry for islet allograft recipients, for 3% crude mortality over a mean of 6 years elapsed follow-up per patient (including periods after complete graft failure and loss to observed follow-up). Causes of death were (# cases): infection (5); cerebral hemorrhage (3); cardiovascular (2); acute respiratory distress syndrome (1); diabetic ketoacidosis (1); lung carcinoma (1); multi-organ failure unknown etiology (1); acute toxicity (1); unknown/unreported causes (3).

Exhibit 7-12
Life-Threatening Events

A.



	1999-2003	2004-2006	2007-2009	p
Life-threatening event	64/246 (26%)	54 / 190 (28%)	14 / 135 (11%)	0.02

B.

Life-Threatening Events (in System/Organ Class Order)

System/Organ Class	MedDRA Preferred Term	Type of Transplant	Era	Months post infusion 1	Related to Infusion Procedure?	Related to Immunosuppression Therapy?
Blood and lymphatic system disorders	Anaemia	ITA	2004-2006	3.3	Unlikely related	Possibly related
	Anaemia	ITA	2004-2006	1.9	Unlikely related	Unlikely related
	Anaemia	IAK/SIK	1999-2003	0.9	Possibly related	Unlikely related
	Anaemia	IAK/SIK	1999-2003	46.6	Not related	Possibly related
	Blood disorder	IAK/SIK	1999-2003	8.5	Not related	Unlikely related
	Lymphopenia	ITA	2004-2006	0.0	Not related	Related
	Lymphopenia	ITA	2004-2006	0.0	Not related	Related
	Lymphopenia	ITA	2004-2006	-1.2	Not related	Related
	Lymphopenia	ITA	2004-2006	0.0	Not related	Related
	Lymphopenia	IAK/SIK	1999-2003	18.6	Unlikely related	Possibly related
Cardiac disorders	Cardio-respiratory arrest	ITA	1999-2003	28.2	Not related	Not related
	Myocardial ischaemia	ITA	1999-2003	0.0	Possibly related	Possibly related
	Myocardial ischaemia	ITA	2007-2010	4.1		
	Myocardial ischaemia	ITA	2007-2010	0.7	Not related	Not related
	Myocardial ischaemia	IAK/SIK	2007-2010	26.7	Unlikely related	Unlikely related
Gastrointestinal disorders	Gastrointestinal haemorrhage	IAK/SIK	2004-2006	0.0	Related	Unlikely related
	Gastrointestinal obstruction	ITA	2004-2006	1.6	Related	Not related
	Peritoneal haemorrhage	ITA	1999-2003	1.1	Related	Possibly related
	Peritoneal haemorrhage	ITA	1999-2003	1.0	Related	Unlikely related
	Peritoneal haemorrhage	ITA	2004-2006	0.0	Related	Not related
	Peritoneal haemorrhage	ITA	2007-2010	6.7	Related	Unlikely related
	Peritoneal haemorrhage	ITA	1999-2003	49.8	Related	Not related
	Peritoneal haemorrhage	ITA	1999-2003	17.2	Related	Not related
	Peritoneal haemorrhage	ITA	2007-2010	8.2	Related	Not related

System/Organ Class	MedDRA Preferred Term	Type of Transplant	Era	Months post infusion 1	Related to Infusion Procedure?	Related to Immunosuppression Therapy?
	Peritoneal haemorrhage	IAK/SIK	1999-2003	0.0	Related	Not related
	Peritoneal haemorrhage	IAK/SIK	2004-2006	15.2	Related	Not related
General disorders and administration site conditions	Death	ITA	2007-2010	19.8	Possibly related	Possibly related
	Death	IAK/SIK	1999-2003	43.9	Not related	Not related
Hepatobiliary disorders	Cholecystitis	ITA	1999-2003	12.4	Possibly related	Unlikely related
	Portal vein thrombosis	ITA	1999-2003	3.3	Related	Not related
	Portal vein thrombosis	ITA	2004-2006	0.0	Related	Not related
Immune system disorders	Hypersensitivity	ITA	2004-2006	29.7	Not related	Related
	Hypersensitivity	ITA	1999-2003	34.0	Unlikely related	Possibly related
	Hypersensitivity	IAK/SIK	1999-2003	10.5	Not related	Unlikely related
Infections and infestations	Infection	ITA	2004-2006	20.7	Not related	Possibly related
	Infection	ITA	2004-2006	33.9	Not related	Possibly related
	Infection	ITA	2004-2006	1.6	Related	Not related
	Infection	ITA	2004-2006	5.9	Possibly related	Possibly related
	Infection	ITA	1999-2003	33.2	Unlikely related	Possibly related
	Opportunistic infection	ITA	2004-2006	60.3	Unlikely related	Related
	Opportunistic infection	IAK/SIK	2007-2010	12.8	Not related	Possibly related
Investigations	Blood alkaline phosphatase	ITA	1999-2003	0.2	Possibly related	Unlikely related
	Blood alkaline phosphatase	ITA	2004-2006	0.1	Possibly related	Unlikely related
	Blood alkaline phosphatase	ITA	2004-2006	0.1	Possibly related	Unlikely related
	Granulocytes abnormal	ITA	1999-2003	1.8	Unlikely related	Related
	Granulocytes abnormal	ITA	1999-2003	1.9	Not related	Possibly related
	Granulocytes abnormal	ITA	1999-2003	37.8	Not related	Related
	Granulocytes abnormal	ITA	1999-2003	2.5	Not related	Possibly related
	Granulocytes abnormal	ITA	1999-2003	26.7	Not related	Possibly related
	Granulocytes abnormal	ITA	1999-2003	1.4	Not related	Possibly related
	Granulocytes abnormal	ITA	1999-2003	9.8	Not related	Related
	Granulocytes abnormal	ITA	1999-2003	4.1	Not related	Possibly related
	Granulocytes abnormal	ITA	1999-2003	1.7	Not related	Possibly related
	Granulocytes abnormal	ITA	1999-2003	49.2	Not related	Possibly related
	Granulocytes abnormal	ITA	1999-2003	0.9	Unlikely related	Possibly related
	Granulocytes abnormal	ITA	1999-2003	0.5	Not related	Possibly related
	Granulocytes abnormal	ITA	1999-2003	19.7	Unlikely related	Possibly related
	Granulocytes abnormal	ITA	1999-2003	0.1	Unlikely related	Possibly related
	Granulocytes abnormal	ITA	1999-2003	0.1	Unlikely related	Possibly related
	Granulocytes abnormal	ITA	2004-2006	0.1	Related	Related
	Granulocytes abnormal	ITA	2004-2006	0.2	Not related	Related
	Granulocytes abnormal	ITA	2004-2006	0.1	Unlikely related	Related
	Granulocytes abnormal	ITA	2004-2006	3.4	Not related	Possibly related
	Granulocytes abnormal	ITA	2004-2006	0.7	Unlikely related	Possibly related
	Granulocytes abnormal	ITA	2004-2006	0.3	Unlikely related	Possibly related
	Granulocytes abnormal	ITA	2004-2006	0.7	Not related	Related
	Granulocytes abnormal	ITA	2004-2006	5.2	Not related	Related
	Granulocytes abnormal	ITA	2004-2006	3.6	Not related	Related
	Granulocytes abnormal	ITA	2007-2010	4.8	Unlikely related	Related
	Granulocytes abnormal	ITA	2007-2010	0.1	Unlikely related	Possibly related
	Granulocytes abnormal	IAK/SIK	1999-2003	3.1	Not related	Possibly related
	Granulocytes abnormal	IAK/SIK	2004-2006	3.8	Not related	Possibly related
	Granulocytes abnormal	IAK/SIK	2004-2006	2.5	Not related	Possibly related
	Granulocytes abnormal	IAK/SIK	2004-2006	7.9	Not related	Possibly related
	Liver function test abnormal	ITA	1999-2003	0.3	Possibly related	Unlikely related
	Liver function test abnormal	ITA	1999-2003	0.2	Possibly related	Unlikely related

System/Organ Class	MedDRA Preferred Term	Type of Transplant	Era	Months post infusion 1	Related to Infusion Procedure?	Related to Immunosuppression Therapy?
	Liver function test abnormal	ITA	1999-2003	0.2	Possibly related	Unlikely related
	Liver function test abnormal	ITA	1999-2003	1.1	Related	Related
	Liver function test abnormal	ITA	1999-2003	0.0	Possibly related	Unlikely related
	Liver function test abnormal	ITA	1999-2003	0.3	Possibly related	Unlikely related
	Liver function test abnormal	ITA	1999-2003	0.2	Possibly related	Unlikely related
	Liver function test abnormal	ITA	1999-2003	0.1	Possibly related	Unlikely related
	Liver function test abnormal	ITA	1999-2003	0.0	Possibly related	Unlikely related
	Liver function test abnormal	ITA	1999-2003	0.1	Possibly related	Unlikely related
	Liver function test abnormal	ITA	1999-2003	0.1	Possibly related	Unlikely related
	Liver function test abnormal	ITA	1999-2003	0.1	Related	Not related
	Liver function test abnormal	ITA	1999-2003	12.9	Possibly related	Unlikely related
	Liver function test abnormal	ITA	1999-2003	0.1	Possibly related	Unlikely related
	Liver function test abnormal	ITA	2004-2006	0.1	Possibly related	Unlikely related
	Liver function test abnormal	ITA	2004-2006	0.3	Possibly related	Unlikely related
	Liver function test abnormal	ITA	2004-2006	0.3	Possibly related	Unlikely related
	Liver function test abnormal	ITA	2004-2006	0.2	Possibly related	Unlikely related
	Liver function test abnormal	ITA	2004-2006	0.0	Possibly related	Unlikely related
	Liver function test abnormal	ITA	2004-2006	0.2	Possibly related	Possibly related
	Liver function test abnormal	ITA	2004-2006	0.1	Possibly related	Possibly related
	Liver function test abnormal	ITA	2004-2006	0.0	Possibly related	Unlikely related
	Troponin I	IAK/SIK	1999-2003	57.1	Not related	Not related
Metabolism and nutrition disorders	Hypoglycaemia	ITA	1999-2003	26.9	Not related	Not related
	Hypoglycaemia	ITA	1999-2003	8.7	Not related	Not related
	Hypoglycaemia	ITA	1999-2003	14.9	Not related	Not related
	Hypoglycaemia	ITA	1999-2003	11.1	Not related	Not related
	Hypoglycaemia	ITA	2004-2006	34.9	Not related	Not related
	Hypoglycaemia	ITA	1999-2003	0.4		Unlikely related
	Hypoglycaemia	ITA	2004-2006	12.4	Not related	Not related
	Hypoglycaemia	ITA	2004-2006	11.3	Not related	Possibly related
	Hypoglycaemia	ITA	2004-2006	2.6	Related	Not related
	Hypoglycaemia	ITA	2004-2006	-8.1	Not related	Not related
	Hypoglycaemia	ITA	2004-2006	0.0	Unlikely related	Unlikely related
	Hypoglycaemia	ITA	2007-2010	16.5	Unlikely related	Unlikely related
	Hypophosphataemia	ITA	2004-2006	2.3	Not related	Possibly related
	Ketoacidosis	ITA	2007-2010	4.5	Possibly related	Unlikely related
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm malignant	ITA	1999-2003	26.9	Not related	Possibly related
	Neoplasm malignant	ITA	2004-2006	4.4	Not related	Not related
	Neoplasm malignant	ITA	2004-2006	22.9	Not related	Possibly related
	Neoplasm malignant	ITA	2004-2006	4.6	Unlikely related	Possibly related
	Neoplasm malignant	ITA	1999-2003	105.0	Not related	Possibly related
Nervous system disorders	Cerebral ischaemia	ITA	1999-2003	0.2	Unlikely related	Unlikely related
	Cerebral ischaemia	IAK/SIK	1999-2003	66.6	Unlikely related	Not related
	Cerebral ischaemia	IAK/SIK	2007-2010	13.2	Not related	Not related
Psychiatric disorders	Insomnia	ITA	1999-2003	19.7	Not related	Related
Renal and urinary disorders	Proteinuria	ITA	2004-2006	24.3	Not related	Related
	Proteinuria	IAK/SIK	2004-2006	28.3	Not related	Possibly related
	Renal failure	ITA	1999-2003	8.1	Unlikely related	Possibly related
Respiratory, thoracic and mediastinal disorders	Aspiration	ITA	2007-2010	0.1	Possibly related	Possibly related
	Pneumonitis	IAK/SIK	1999-2003	0.6	Not related	Possibly related
Vascular disorders	Haematoma	ITA	2004-2006	0.0	Related	Not related

System/Organ Class	MedDRA Preferred Term	Type of Transplant	Era	Months post infusion 1	Related to Infusion Procedure?	Related to Immunosuppression Therapy?
	Haematoma	IAK/SIK	1999-2003	0.0	Related	Not related
	Haemorrhage	ITA	1999-2003	0.0	Possibly related	Unlikely related
	Haemorrhage	IAK/SIK	2004-2006	5.4	Related	Unlikely related
	Hypertension	ITA	1999-2003	50.0	Not related	Possibly related

C. Outcomes of life-threatening events		Total	Outcome				
			Fatal	Not recovered	Recovered	Recovered with seq	Unknown
		N	Row%	Row%	Row%	Row%	Row%
System/Organ Class	Preferred Term						
Blood and lymphatic system disorders	Anaemia	4	.	.	100.0	.	.
	Blood disorder	1	.	.	100.0	.	.
	Lymphopenia	5	.	.	100.0	.	.
Cardiac disorders	Cardio-respiratory arrest	1	100.0	.	.	.	.
	Myocardial ischaemia	4	.	.	50.0	50.0	.
Gastrointestinal disorders	Gastrointestinal haemorrhage	1	.	.	100.0	.	.
	Gastrointestinal obstruction	1	.	.	100.0	.	.
	Peritoneal haemorrhage	9	.	.	100.0	.	.
General disorders and administration site conditions	Death	2	100.0	.	.	.	.
Hepatobiliary disorders	Cholecystitis	1	.	.	100.0	.	.
	Portal vein thrombosis	2	.	.	100.0	.	.
Immune system disorders	Hypersensitivity	3	.	.	33.3	33.3	33.3
Infections and infestations	Infection	5	.	.	40.0	60.0	.
	Opportunistic infection	2	.	.	100.0	.	.
Investigations	Blood alkaline phosphatase	3	.	.	100.0	.	.
	Granulocytes abnormal	30	.	3.3	96.7	.	.
	Liver function test abnormal	22	.	.	95.5	4.5	.
	Troponin I	1	.	.	100.0	.	.
Metabolism and nutrition disorders	Hypoglycaemia	12	.	.	100.0	.	.
	Hypophosphataemia	1	.	.	100.0	.	.
	Ketoacidosis	1	.	.	100.0	.	.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm malignant	5	.	40.0	20.0	40.0	.
Nervous system disorders	Cerebral ischaemia	3	.	33.3	.	66.7	.
Psychiatric disorders	Insomnia	1	.	.	100.0	.	.
Renal and urinary disorders	Proteinuria	2	.	50.0	50.0	.	.
	Renal failure	1	.	.	.	100.0	.
Respiratory, thoracic and mediastinal disorders	Aspiration	1	.	.	100.0	.	.
	Pneumonitis	1	100.0	.	.	.	.
Vascular disorders	Haematoma	2	.	.	100.0	.	.
	Haemorrhage	2	.	.	100.0	.	.
	Hypertension	1	.	.	100.0	.	.

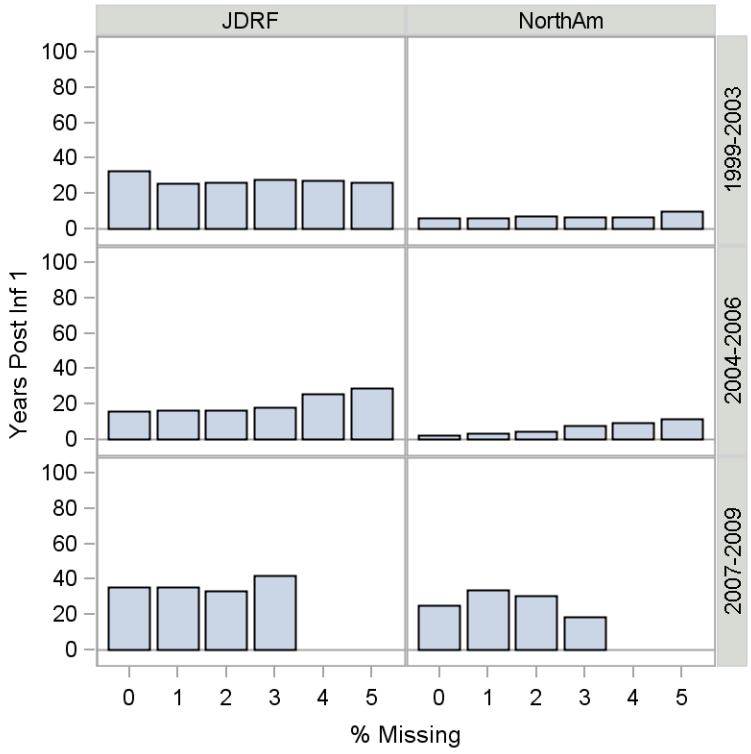
Chapter 8
Registry Data Quality Review

Total number of patients expected at each follow-up visit post last infusion

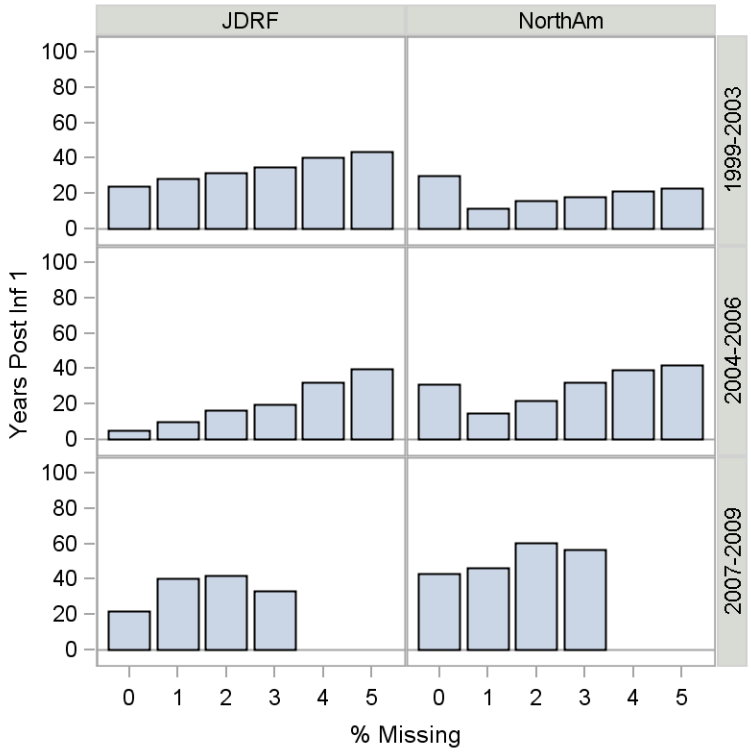
Ns	Overall						JDRF						NorthAm					
	Post LastTx						Post LastTx						Post LastTx					
	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
1999-2003	246	237	232	226	220	213	80	74	73	72	70	69	166	163	159	154	150	144
2004-2006	190	184	176	167	158	107	64	62	61	61	59	38	126	122	115	106	99	69
2007-2009	135	119	67	28	.	.	51	45	24	12	.	.	84	74	43	16	.	.

The bar charts in this Chapter show the percent of expected data that is available at each major time point post last infusion. The highest levels of reporting are on insulin use, which is based on patient diaries, and fasting C-peptide levels. For insulin use, prior complete graft loss is used to impute that the recipient has returned to insulin use, further increasing the available information. Similarly, for fasting C-peptide, a report of complete graft loss with no subsequent re-infusion is used to impute fasting C-peptide of 0 ng/mL, further increasing the availability of C-peptide data. Missing data increases with longer follow-up and in the most recent cohort

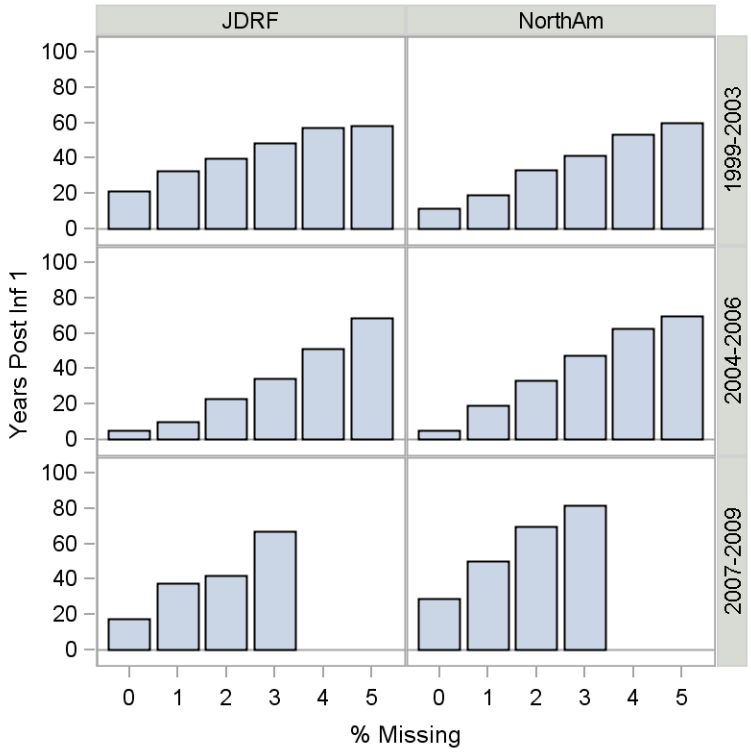
Missing Data for Insulin Independence by Era and Type of Transplant



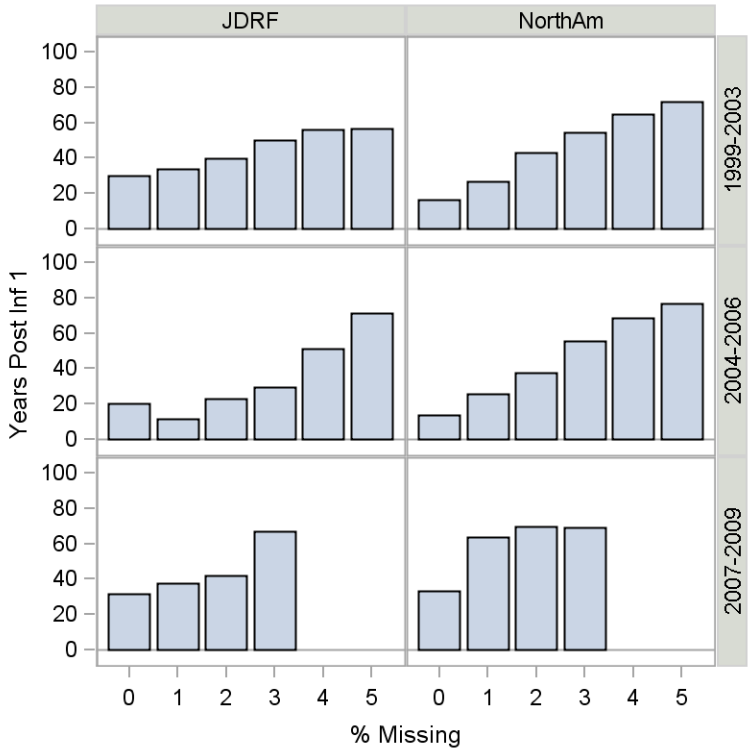
Missing Data for Fasting C-Peptide by Era and Type of Transplant



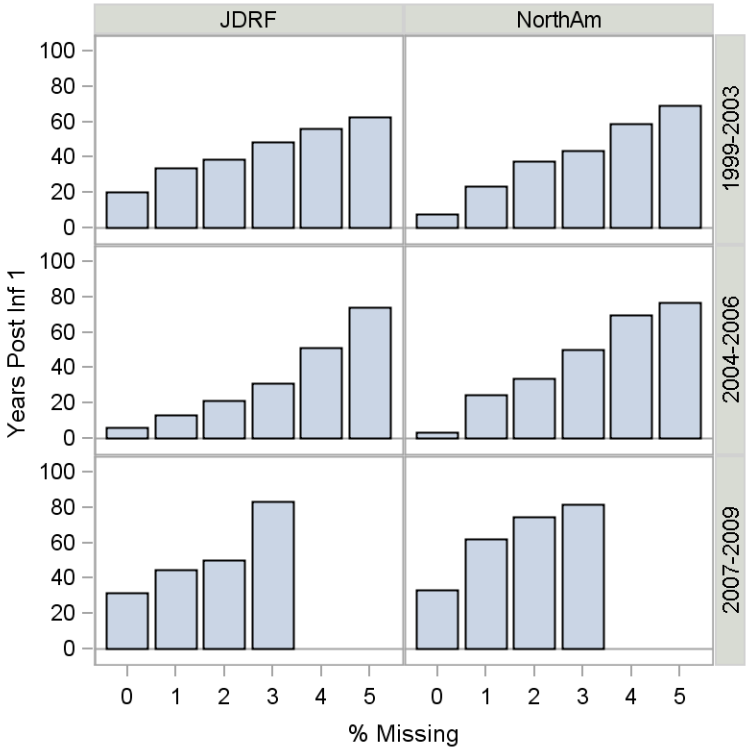
Data for Hemoglobin A1c by Era and Type of Transplant



Missing Data for Fasting Blood Glucose by Era and Type of Transplant



Missing Data for Severe HypoGlycemia by Era and Type of Transplant



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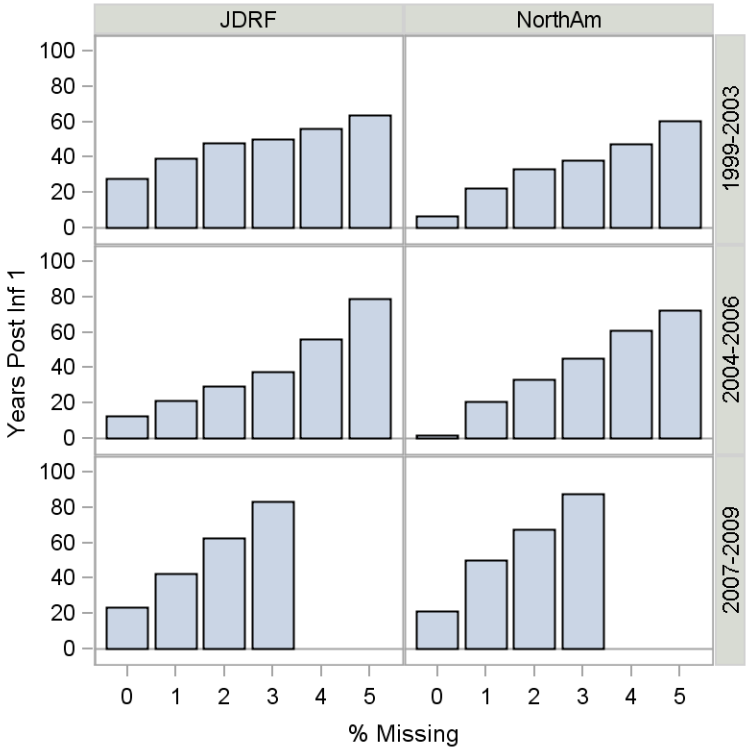
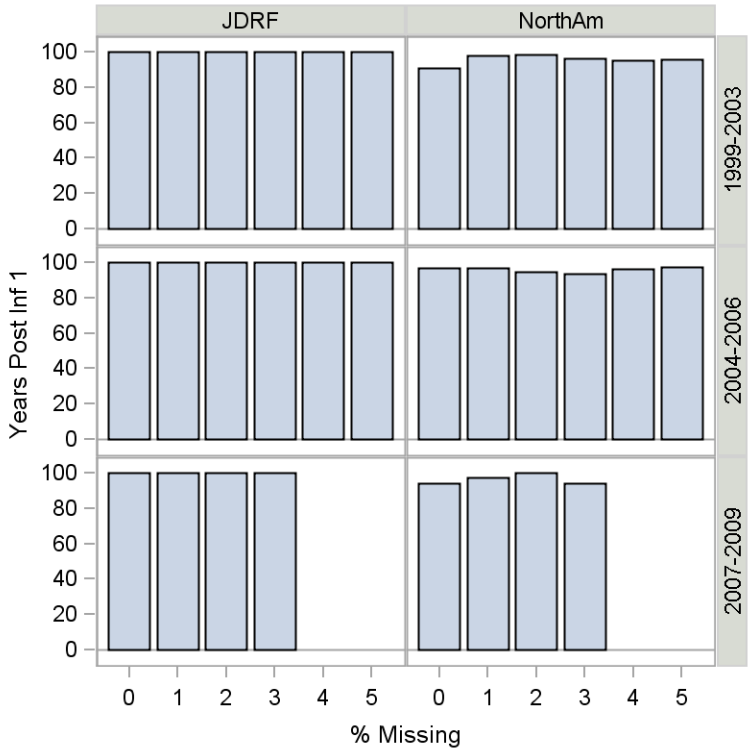
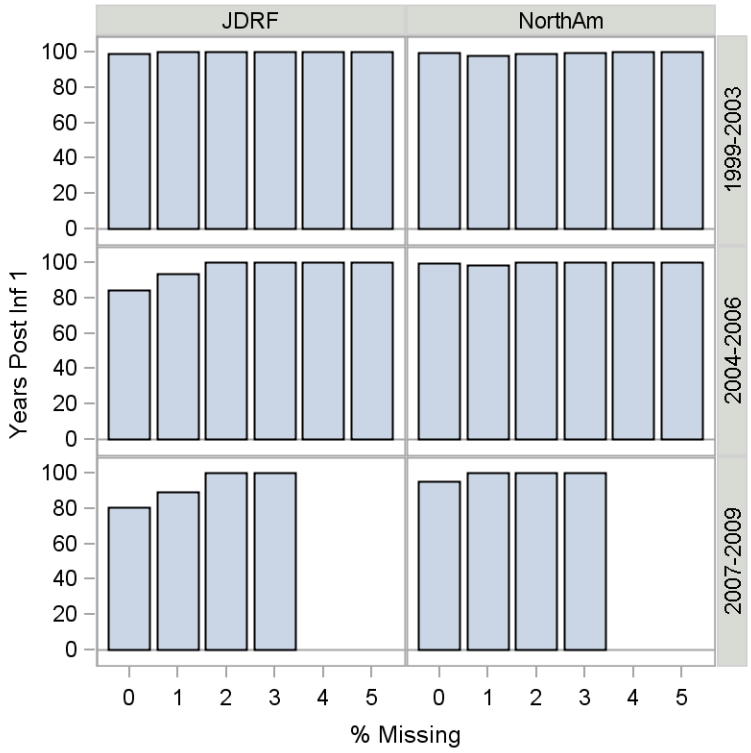


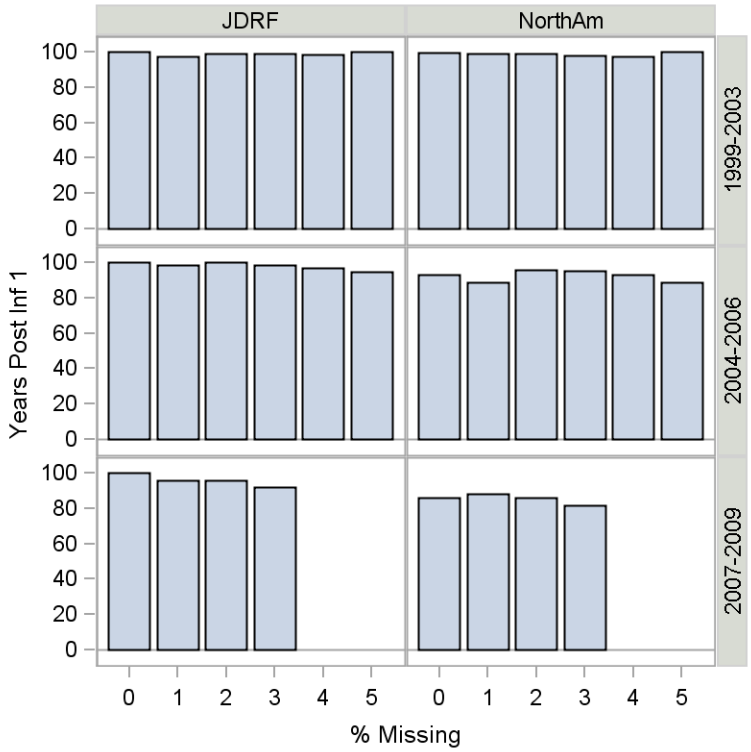
Missing Data for Clarke Score by Era and Type of Transplant



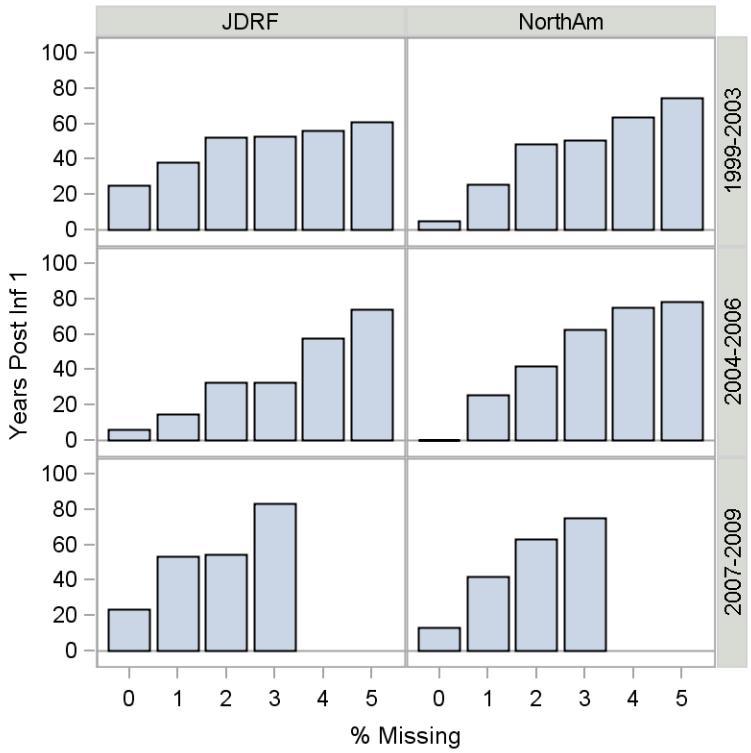
Missing Data for Ryan Hypo by Era and Type of Transplant



Missing Data for C-Peptide AUC by Era and Type of Transplant



Missing Data for Cockcroft-Gaullt by Era and Type of Transplant



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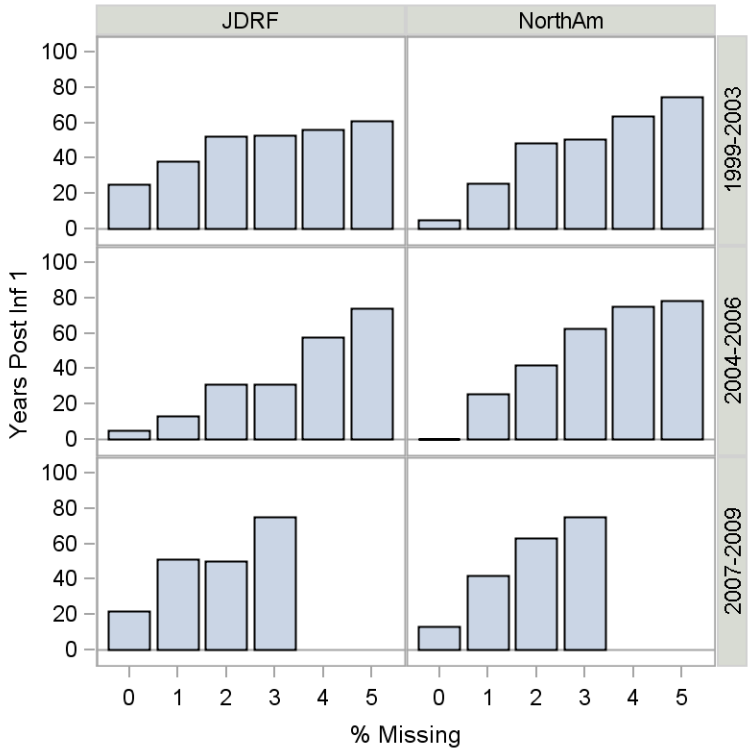
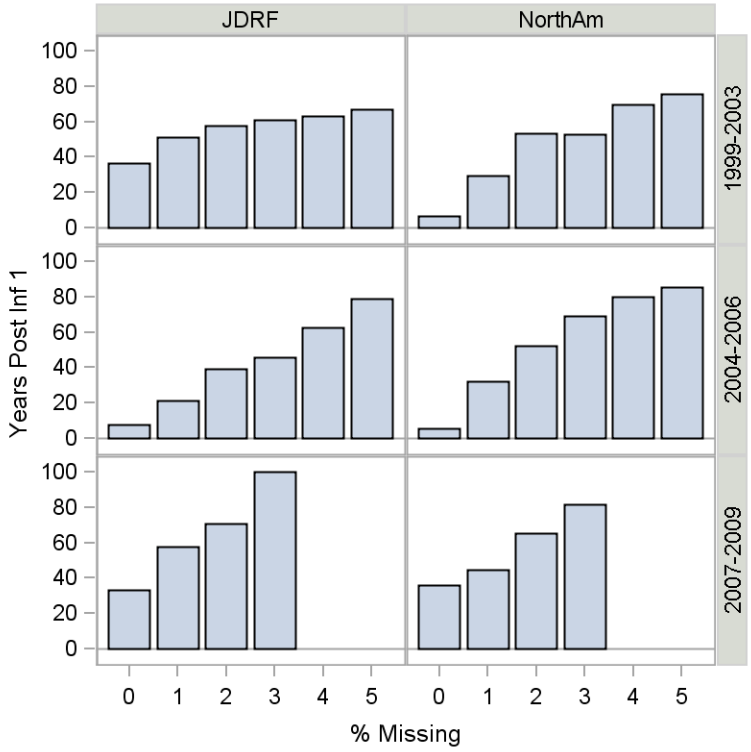


Missing Data for Cholesterol by Era and Type of Transplant



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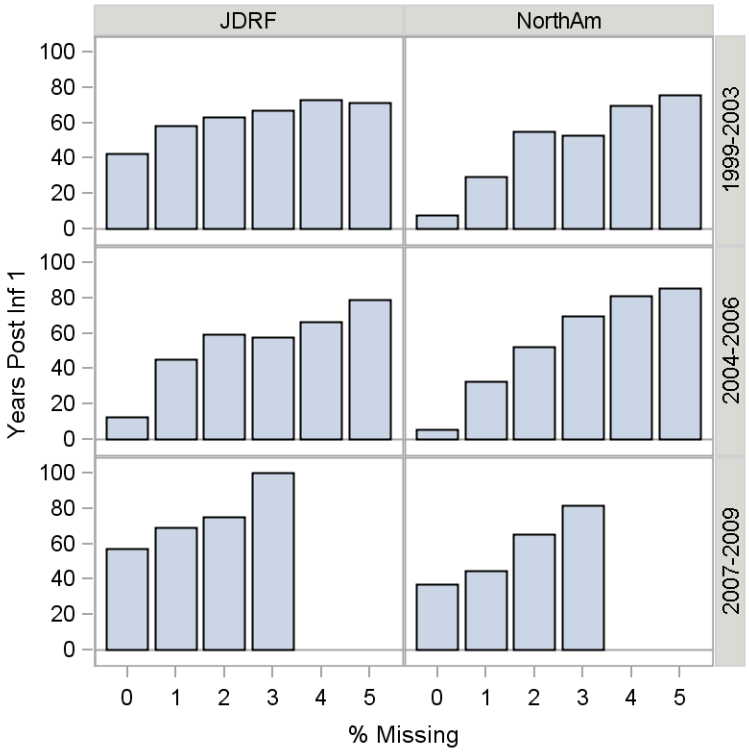
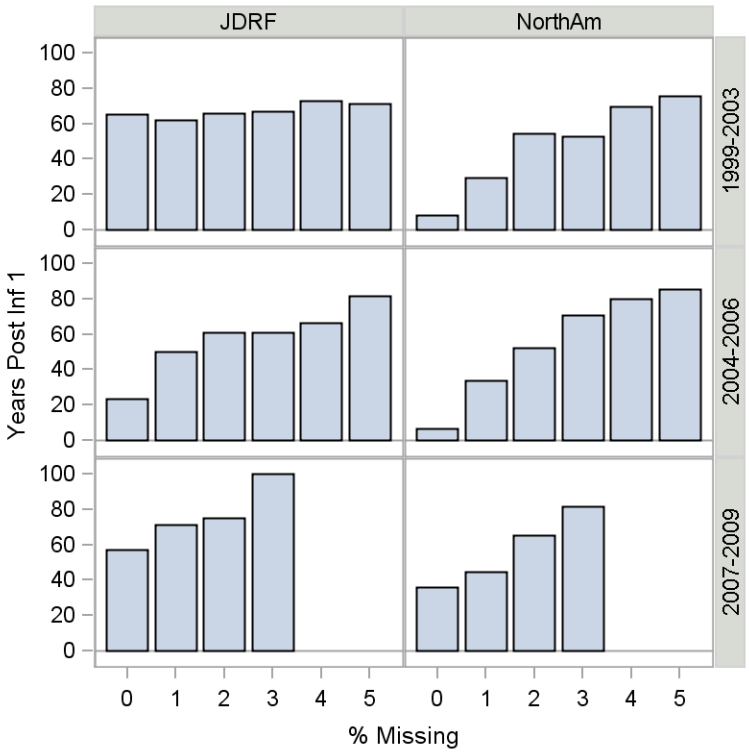
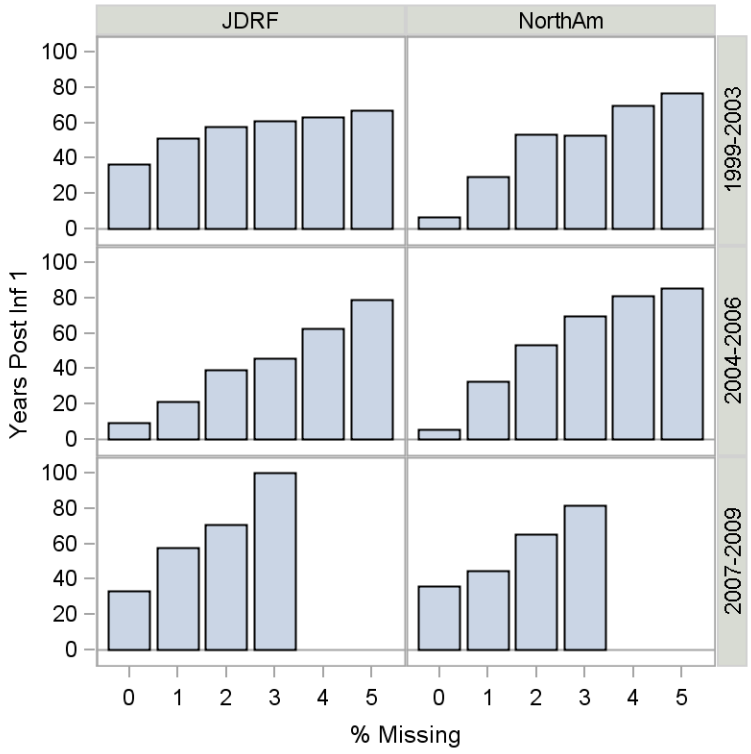


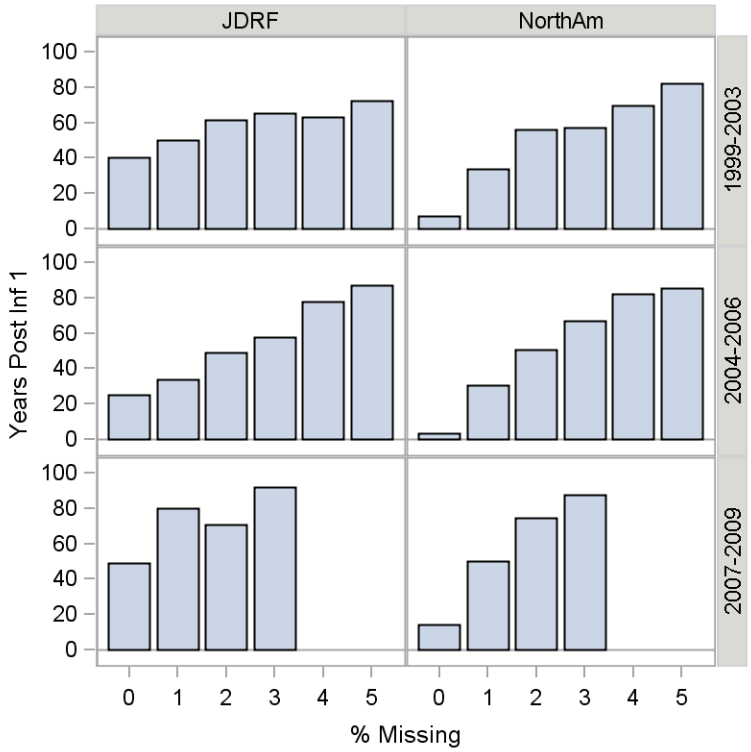
Missing Data for LDL by Era and Type of Transplant



Missing Data for Triglycerides by Era and Type of Transplant



Missing Data for Bilirubin by Era and Type of Transplant



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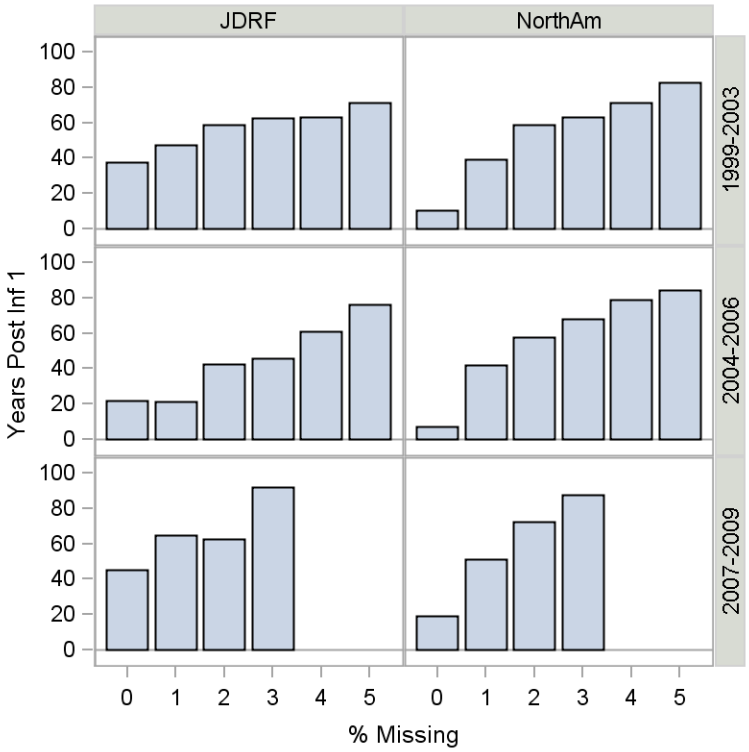
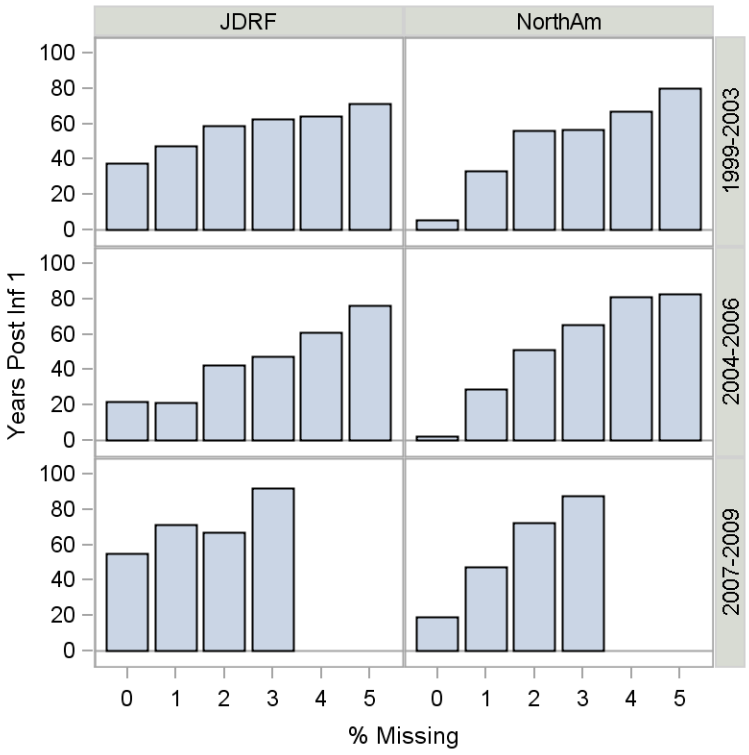
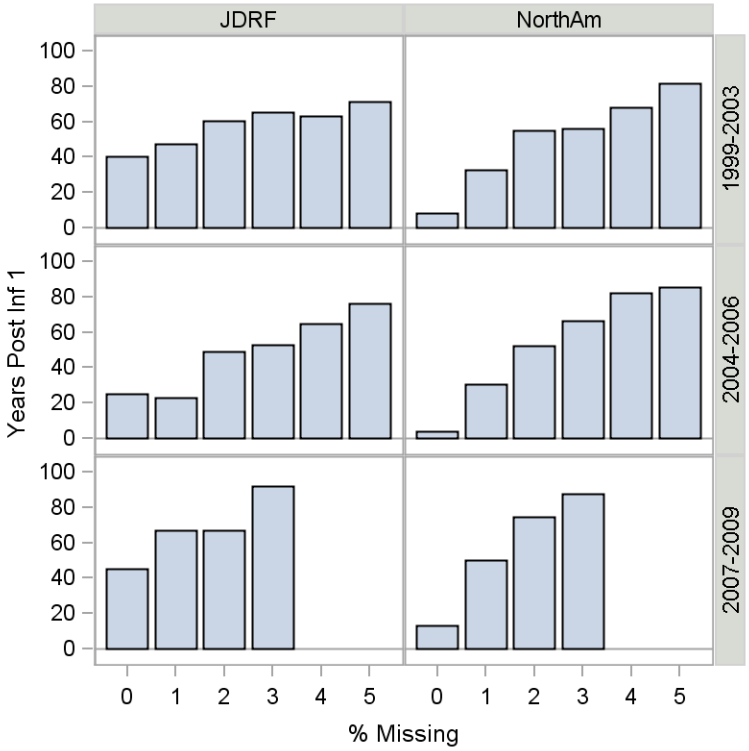


Missing Data for AST by Era and Type of Transplant



Missing Data for Alkaline Phosphate by Era and Type of Transplant



Appendix A
Islet Transplant Centers, Coordinating Center and CITR Committees
Islet Transplant Centers

(Centers and Staff are listed in alphabetical order)

Baylor College of Medicine/ The Methodist Hospital
Houston, Texas, USA
PI: John A. Goss
Cheryl Durkop
Tiffany Zgabay

Baylor Regional Transplant Institute
Dallas, Texas, USA
PI: Marlon Levy
Darrell Grimes
Bashoo Naziruddin
Lori Otken
Kerri Purcell

Benaroya Research Institute
Seattle, Washington, USA
PI: Carla Greenbaum
Marli McCulloch-Olson
Marilyn Reeve

Carolinas Medical Center
Charlotte, North Carolina, USA
PI: Paul Gores
Melissa McGraw

Center for Islet Transplantation at Harvard Medical School
Boston, Massachusetts, USA
PI: Enrico Cagliero
Kerry

Columbia University
New York, New York, USA
PI: Mark A. Hardy
Joan Kelly
Piotr Witkowski

Emory Transplant Center
Atlanta, Georgia, USA
PI: Mark Rigby
Jenny Joseph
Elizabeth Holbrook
Jennifer Hutchinson
Marti Sears

GenevaGRAGIL Network
Geneva, Switzerland
PI: Thierry Berney
Elsa Boely
Coralie Brault
Sandrine Demuylder-Mischler
Laure Nasse

Mayo Clinic
Rochester, Minnesota, USA
PI: Yogish Kudva
Jarrett Anderson
LeAnn Batterson
Deborah Dicke-Henslin
Jane Fasbender
Michelle Kreps

NIH Clinical Transplant Center
Bethesda, Maryland, USA
PI: David Harlan
Eric Liu
Pat Swanson

Lille University Hospital
Lille Cedex, France
PI: Francois Pattou
Rimed Ezzouaoui
Valery Gmyr
Julie Kerr-Conte
Violeta Raverdy
Marie Christine Vantyghem

Northwestern University
Chicago, Illinois, USA
PI: Dixon Kaufman
Patrice Al-Saden
Elyse Stuart

San Raffaele Institute
Milan, Italy
PI: Antonio Secchi
Marina Scavini
Paola Maffi
Paola Magistretti

Scripps Health
La Jolla, California, USA
PI: Christopher Marsh
Denadra Holland

Southern California Islet Consortium (SCIC)
Duarte, California, USA
PI: Fouad Kandeel
Jeannette Hacker
Lisa Johnson
Jeffrey Longmate
Aria Miller
Keiko Omori
Chris Orr
Cindy Stahl

St. Vincent's Institute
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