

## ***Scientific Summary of the Collaborative Islet Transplant Registry (CITR) 2020 Eleventh Allograft Data 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 1.9 million people in the US have Type 1 diabetes mellitus, with this number expected to rise to 5 million by the year 2050. 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. From 2005 through 2015 the Clinical Islet Transplant Consortium ([www.CITIsletStudy.org](http://www.CITIsletStudy.org)) conducted studies designed 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 from all such programs have contributed data and collaborated 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](http://www.clinicaltrials.gov). In addition, CITR maintains interactive maps of North American and JDRF European and Australian islet transplant programs at [www.citregistry.org](http://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 from 2006 through 2015. The cumulated North American, Eurasian and Australian data are pooled for analyses included in the annual report. CITR Annual Reports are publicly available as open access and can be downloaded at [www.citregistry.org](http://www.citregistry.org). **This Scientific Summary highlights results from the CITR 2020 (11<sup>th</sup>) Allograft Data Report, either by direct inclusion or by reference.**

### **PATIENTS AND METHODS**

From 1999 through 2020 – the cut-off for the 11<sup>th</sup> Annual Report – CITR has collected data on the following groups of study subjects:

- Allogeneic islet transplantation (typically cadaveric donor), performed as either islet-transplant alone (ITA) or islet-after-kidney (IAK). A small number of cases have been performed as islet simultaneous with kidney (SIK) or kidney-after-islet (KAI). SIK and KAI

are included in the safety profile presented in Chapter 7 of this report, but were otherwise excluded from analyses to reduce heterogeneity in the transplant groups (SIK and KAI are more similar to ITA than IAK in terms of immunosuppression, but also similar to IAK in terms of kidney transplant).

- Autologous islet transplantation, performed after total pancreatectomy are also reported to CITR. They are summarized in a separate report.

The 11<sup>th</sup> Annual Report and this Summary focus on the allogeneic islet transplant recipients. The autologous islet transplant recipients are the subject of a separate report.

**The database for the 10<sup>th</sup> Annual Report was closed for analysis on February 15, 2022 for data on recipients that were first transplanted as of December 15, 2020.**

At the time of their first Islet transplant,

- ITA recipients were 14-74 years of age (mean 47±10.9SD), had T1DM for 2-61 (30±11.7) years, and 73% had very poor diabetes control including hypoglycemia unawareness. 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<sub>1c</sub> levels (>8% of total hemoglobin).
- IAK recipients were 28-69 years of age (mean 48±8.9SD), had T1DM for 7-56 (35±9.2) years, and 46% had very poor diabetes control including hypoglycemia unawareness.
- SIK recipients were 6-70 years of age (mean 50±11.7SD), had T1DM for 2-66 (34±13.2) years, and 10% had very poor diabetes control including hypoglycemia unawareness.

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 28, 75, Month 6, and annually post infusion. At each new infusion, a new follow-up schedule is established.

As of 2021, by decision of the Executive Committee, only serious adverse events (regardless of grade) are reportable to CITR. A copy of the CITR data collection forms may be requested from the CITR Coordinating Center ([citr@emmes.com](mailto:citr@emmes.com)), or viewed at the CITR website ([www.citregistry.org](http://www.citregistry.org)).

CITR utilizes the Coordinating Center's (The Emmes Company, LLC, Rockville, MD; [www.emmes.com](http://www.emmes.com)) web-based data entry and management systems to capture data on recipients, donors and pancreata. Additional data are obtained through data sharing agreements with the United Network for Organ Sharing (UNOS) for US donor data, the Administrative and Bioinformatics Coordinating Center (ABCC, 2001-2009) of the Islet Cell Resource Centers for the islet data, and the Data Coordinating Center of the Clinical Islet Transplant Consortium (CIT, 2005-2015).

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.

### **Statistical Analysis.**

In addition to updating information on total islet transplant procedures and descriptions of the recipient, donor, islet and immunosuppression data, a major focus of the present analyses is to continue identifying and corroborating factors of patient selection, islet processing and islet transplantation management 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 are routinely performed as scheduled and include data audits for key recipient baseline, primary outcome, and safety 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.

First achievement of insulin independence, as well as complete graft failure, were 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.

Primary outcomes, analyzed as prevalence (percent) at annual study time points post last infusion, include:

- Insulin independence ( $\geq 14$  consecutive days)
- C-peptide  $< 0.3$  ng/mL
- HbA1c  $< 7.0\%$
- Fasting blood glucose of 60-140, and
- Absence of severe hypoglycemic events
- Combined HbA1c  $< 7.0\%$  and absence of severe hypoglycemic events

An “all-factors-on-all-outcomes” analytical approach was undertaken to uncover the most predictive recipient, donor, islet and medical management practices associated with the greatest success rates in the primary outcomes, within each of ITA and IAK. Analysis of IAK is the subject of a forthcoming publication. Every variable available on recipient, donor, islet, and immunosuppression was analyzed univariately to determine its effect on each outcome with significance determined at  $p < 0.01$ .

Secondary outcomes include whole-distribution description of laboratory measurements, metabolic test results, liver and kidney function measures, and complications of diabetes.

Safety is monitored by incidence rates of serious adverse events classified by CIT-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.

Statistical analyses were conducted using SAS 9.4.

## RESULTS

**Islet Allograft Transplantation Activity 1999-2020.** As of December 15, 2020, the CITR Registry included data on 1,399 allogeneic islet transplant recipients (1,108 islet transplant alone, ITA, and 236 islet after kidney, IAK, 49 simultaneous islet kidney, SIK, and 6 kidney after islet, KAI), who received 2,832 infusions from 3,326 donors (Exhibit 1). The North American sites contributed 48% of recipients, while the Eurasian and Australian sites contributed 52%. Combining the ITA and IAK recipients, 27% received a single islet infusion, 49% received two, 21% received three, and 4% received 4-6 infusions.

**Exhibit 1**  
**CITR Recipients, Infusions and Donors by NIDDK/JDRF Sites and by ITA/IAK/SIK/KAI Consented, Registered and First Infused in 1999-2020**

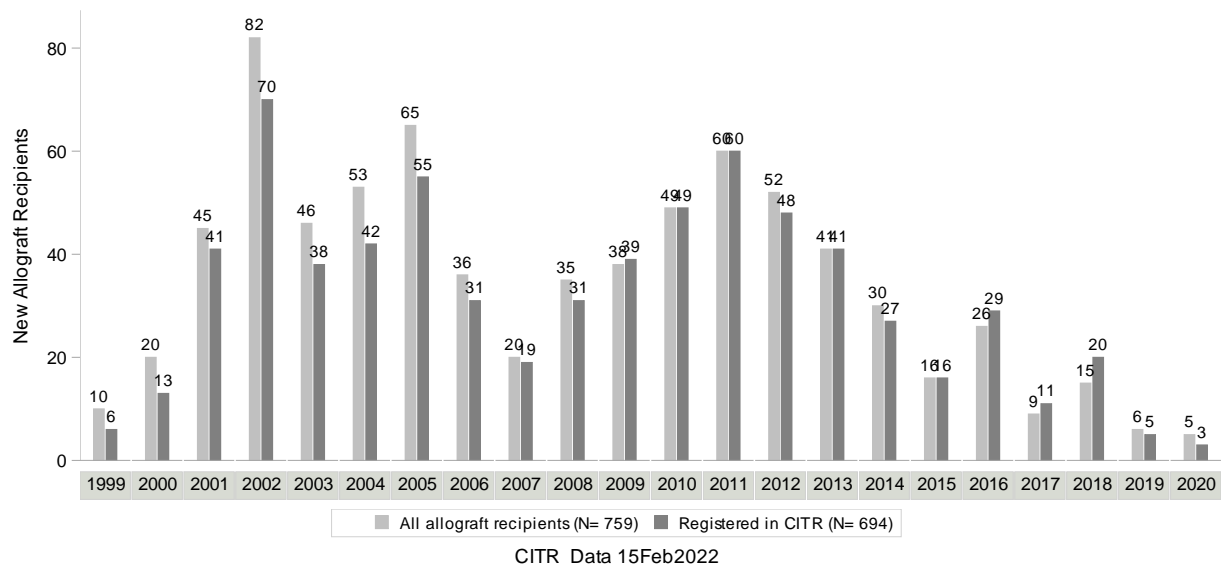
	Islet Transplant Alone (ITA)			Islet After Kidney (IAK)			Simultaneous Islet Kidney (SIK)			Kidney After Islet (KAI)			GRAND TOTALS
	Total	North America	Europe/Australia/Asia	Total	North America	Europe/Australia/Asia	Total	North America	Europe/Australia/Asia	Total	North America	Europe/Australia/Asia	
Recipients	<b>1,108</b>	579	529	<b>236</b>	86	150	<b>49</b>	1	48	<b>6</b>	3	3	<b>1,399</b>
Infusions	<b>2,284</b>	1,208	1,076	<b>440</b>	157	283	<b>95</b>	1	94	<b>13</b>	7	6	<b>2,832</b>
Donors	<b>2,719</b>	1,271	1,448	<b>496</b>	167	329	<b>98</b>	1	97	<b>13</b>	7	6	<b>3,326</b>

Exhibits 2A and 2B display the data collected from the islet transplant programs in North America and the JDRF Eurasian and Australian sites from 1999 through 2015. Of the 759 total North American recipients reported by general survey of the sites to have received an islet allograft in 1999-2020, 694 (91%) consented to and were registered in CITR. Of the 761 total reported JDRF Eurasian and Australian recipients, 96% (732) were consented and registered in CITR. Both North American and JDRF sites saw a decline in new recipients around 2007, followed by an increase in following years which peaked in 2011 for North American sites and in 2012 for JDRF sites. Both North American sites and JDRF sites again saw a decline in the number of new recipients over the 2013 to 2020 period.

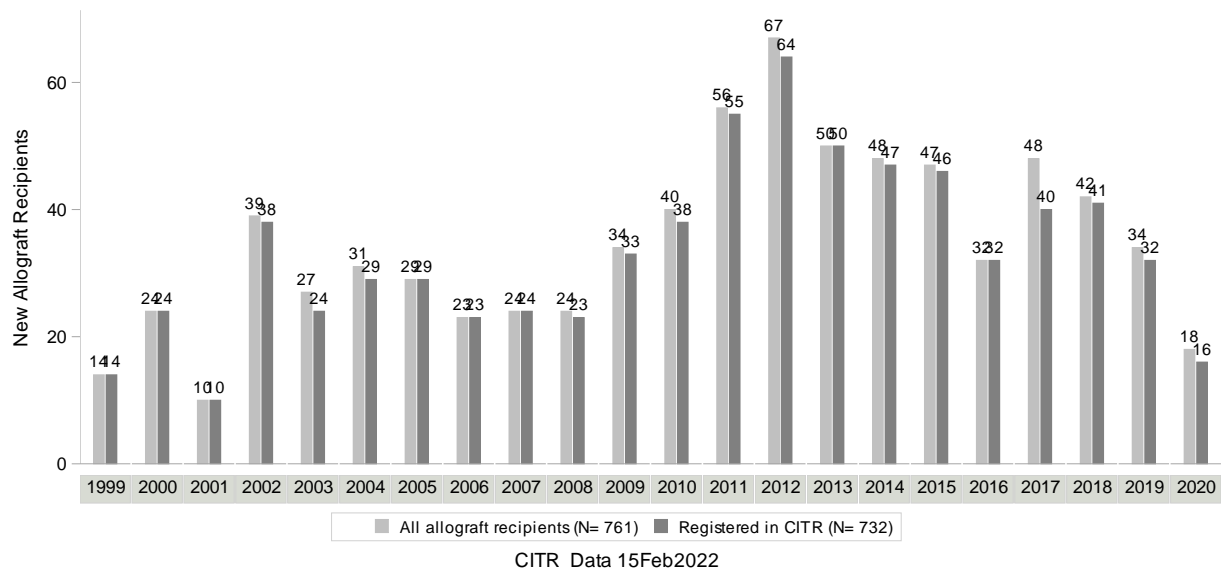
**Exhibit 2**

**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 CITR North American Centers 1999-2020**



**B. Allograft recipients at CITR Eurasian and Australian Centers 1999-2020**



**Islet Transplant Recipient Characteristics.** Over the eras of the Registry, the following trends are observed for recipients of allogeneic islets:

- Recipients have been selected at older age (42±0.6\* to 52±1.6) and longer wait time (238±22days to 456±71days) at initial transplant
- Recipients have been selected with increased use of insulin pump (31% to 57%)

- Greater proportions had positive GAD65 autoantibody (34% to 60%)
- Recipients had lower levels of total cholesterol ( $181\pm 3$  to  $166\pm 8$ ) and LDL cholesterol ( $99\pm 3$  to  $86\pm 8$ ) in recent eras

\*Mean $\pm$ SE

There were also notable differences in medical characteristics between ITA and IAK recipients, most notably, a much lower prevalence of hypoglycemia unawareness, and much lower initial eGFR in the IAK ( $62.2\pm 1.5$  vs.  $91.3\pm 0.7$ ) recipients.

**Donor Information.** All allograft donors were deceased. Donor weight and BMI have increased substantially over the eras, from  $28.1\pm 0.3$  BMI in 1999-2002 to  $31.9\pm 1.6$  in 2019-2022. Infusions (an “infusion” is defined as all islet products from one, two or three (maximum) donors given to a single recipient on a single day) were comprised of about 57% all male donors, 39% all female donors, and 4% mixed male and female donors. About 19% of infusions derived from Hispanic donors, while about 10% derived from non-white donors. About 61% of the donors had cerebrovascular accident/stroke as their cause of death while 24% experienced trauma.

About 28% of the donors received a transfusion during their terminal hospitalization, while only 6% received a transfusion intraoperatively. Sixty-seven percent (67%) of the donors received steroids and 81% received at least one vasopressor during the terminal hospitalization. Significantly fewer donors received a vasopressor in recent eras, declining from 97% in 1999-2002 to 42% in 2019-2022. Insulin was administered during recovery to 49%. A total of 13 donors tested positive for anti-HBC, three tested positive for RPR-VDRL and two for HCV. Mean serum creatinine of the donors has decreased slightly from  $1.2\pm 0.1$  to  $0.9\pm 0.1$  mg/dL over the eras of the registry. Mean maximum stimulated blood glucose decreased from  $244\pm 6$  SE to  $195\pm 20$  mg/dL over the eras.

**Islet product characteristics.** Total cell volume infused has declined appreciably over the eras ( $4.0\pm 0.1$  in 1999-2002 to  $3.3\pm 0.1$  in 2015-2018). Total IEQs declined somewhat in the most recent era, but IEQ/Kg recipient have remained remarkably stable. Endotoxin (both total and /kg) has declined sharply over the eras ( $27.8\pm 4.6$  to  $2.4\pm 0.7$  for total). Stimulation index has declined over the eras ( $3.8\pm 0.3$  to  $2.8\pm 0.4$ ) as has islet viability ( $91.2\pm 0.5$  to  $87.8\pm 1.0$ ).

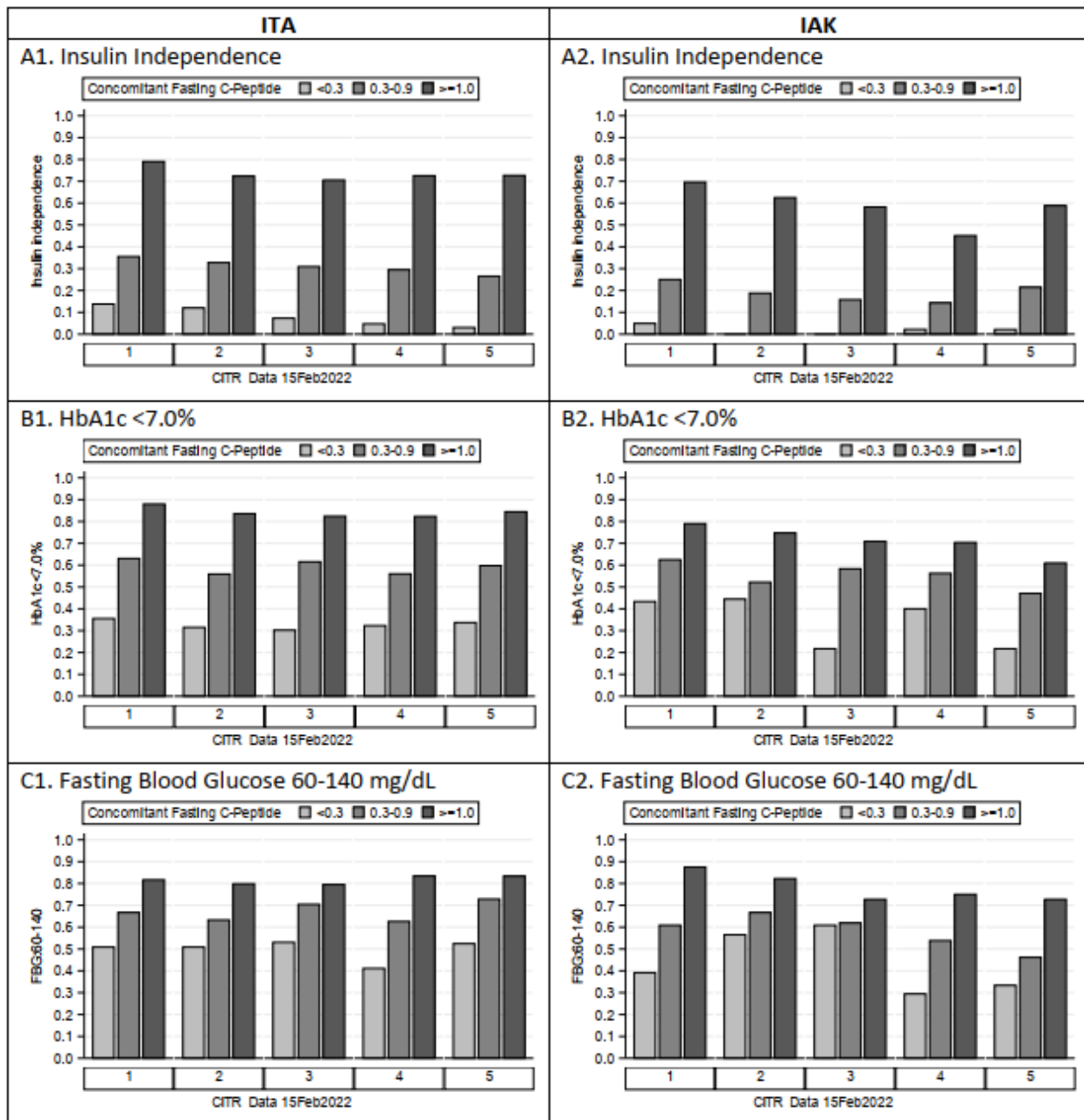
**Immunosuppression therapy.** Induction with IL2R antagonists only, which comprised about 53% of all initial infusions in 1999-2002, was replaced or supplemented with regimens that included T-cell depletion with/without TNF antagonists in about 67% of the new infusions performed since 2015. In 1999-2002, maintenance immunosuppression was predominantly (64%) calcineurin (CNI)+mTOR inhibitors. It was increasingly replaced or supplemented throughout the eras by a CNI and IMPDH-inhibitor combination; in the most recent era, CNI+mTOR inhibitors were used in 15% of new infusions while CNI+IMPDH inhibitors were used in about 62%.

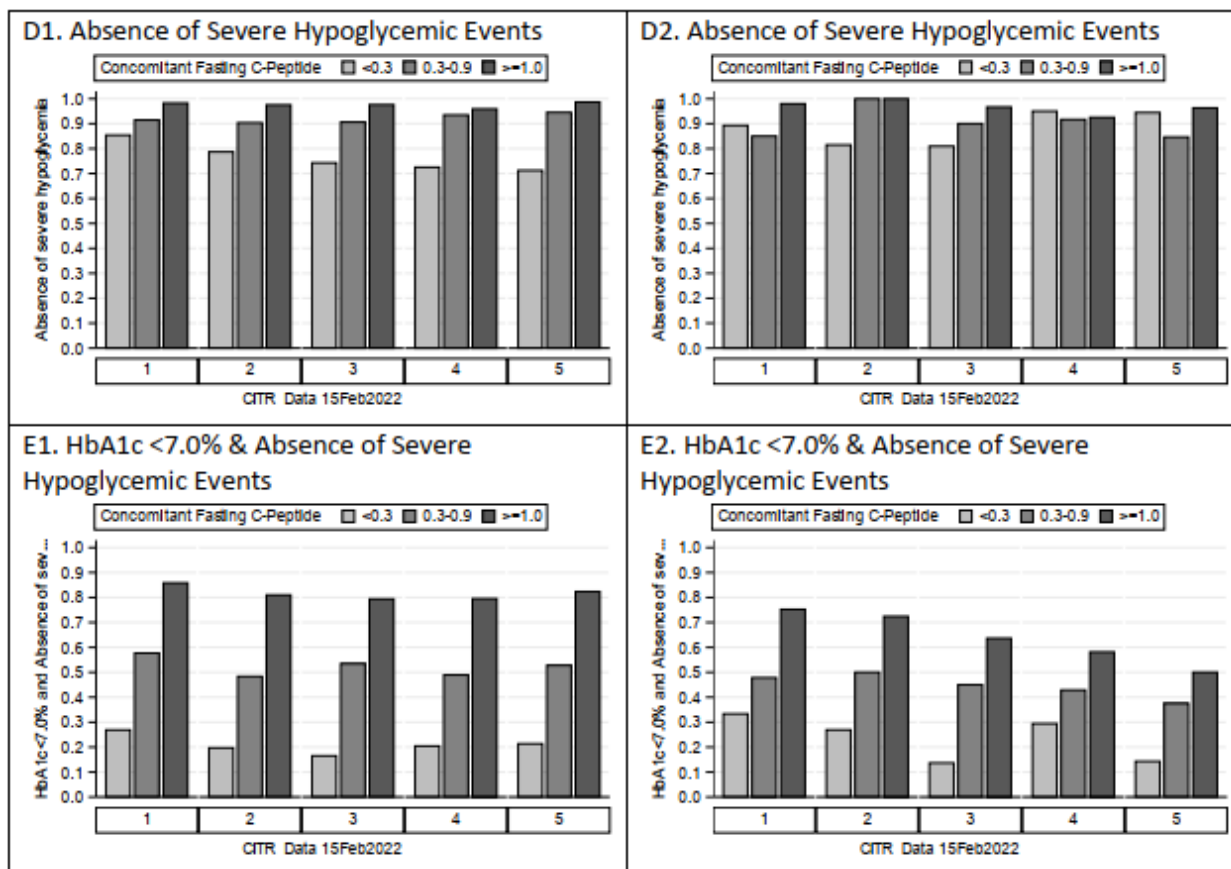
**Graft Function.** First achievement of insulin independence measured from initial islet infusion, with or without subsequent infusion, is an indicator of the rate of engraftment under real-time conditions that include early graft loss, islet resource availability, patient/doctor decisions and myriad 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.

The primary endpoints are analyzed as prevalence at annual time points post last infusion to isolate the factors that optimized the outcomes.

In both transplant groups, the higher the fasting C-peptide level, the higher the likelihood of insulin independence, HbA1c<7.0%, FBG of 60-140, and the lower the likelihood of severe hypoglycemia (Exhibit 3). 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 is drastically reduced over all follow-up even with C-peptide<0.3 ng/mL.

**Exhibit 3**  
**Association of Fasting C-Peptide Level (ng/mL) with Other Primary Outcomes at Years 1-5 Post Last Infusion**



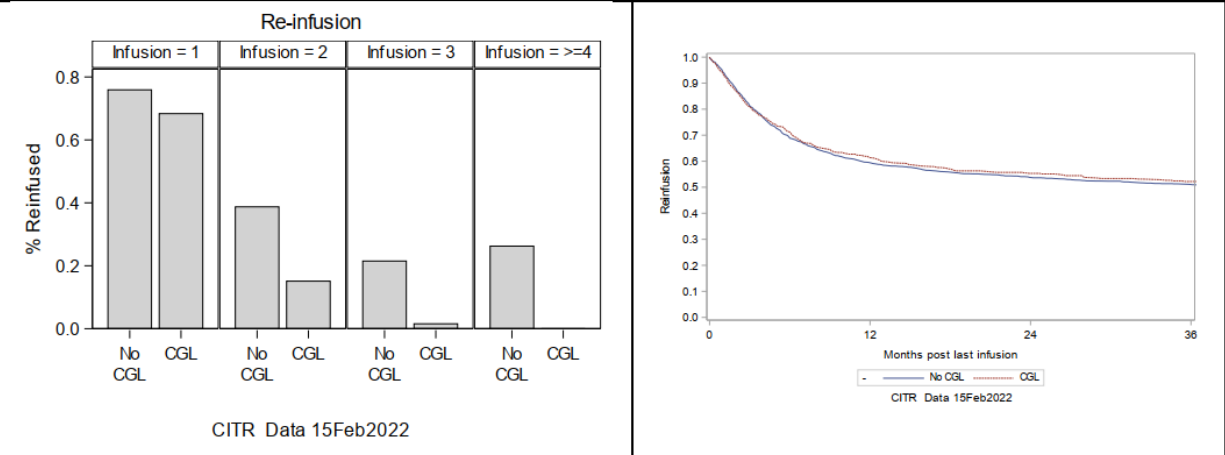


Over the years of the CITR data, re-infusion (Exhibit 4) has been performed in about 73% of all allograft recipients. It may have been performed after complete graft failure, or while the recipient still had at least some graft function (C-peptide  $\geq 0.3$  ng/mL), or even while the patient was fully insulin independent. The group most likely to be re-infused was those who were not insulin independent (Exhibit 4B). This Kaplan-Meier also shows that time to re-infusion varied substantially from days to years, with a mean  $\pm$  SD of  $13 \pm 22$  months. Rates of second infusion by era show a substantially uniform rate over the eras (Exhibit 4C) and did not differ significantly by transplant type (Exhibit 4D).

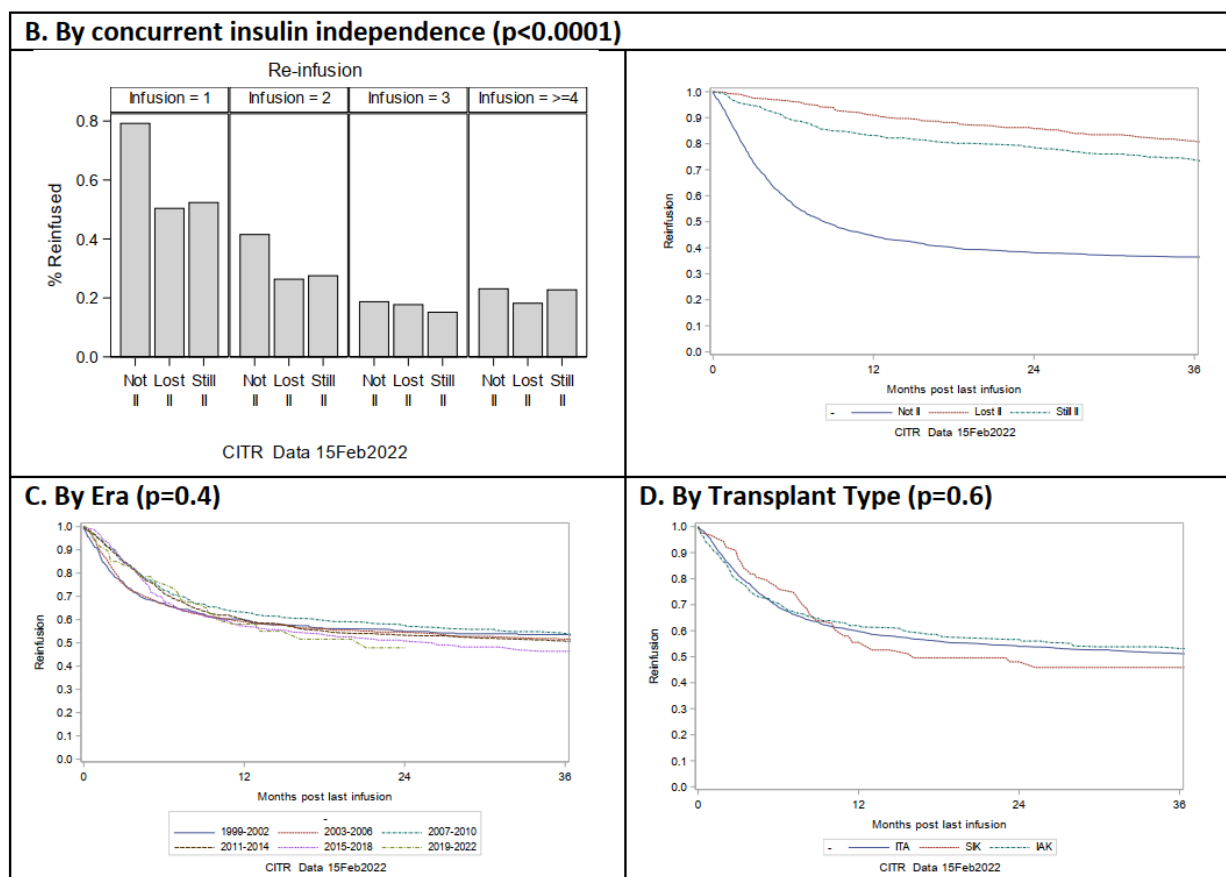


### Exhibit 4 Re-infusion (Kaplan-Meier), over all infusions

#### A. By previous complete graft loss (CGL) (p=0.2)



	<i>Reinfusion</i>		
	<i>No</i>	<i>Yes</i>	<i>Total</i>
	<i>N</i>	<i>N</i>	<i>N</i>
<i>Infusion 1</i>	335	926	1261
<i>Infusion 2</i>	605	321	926
<i>Infusion 3</i>	265	56	321
<i>Infusion ≥4</i>	56	16	72
<i>All</i>	1261	1319	2580



**Adverse Effects (laboratory determinations and reported adverse events).** Data collection on serious adverse events and other effects of islet transplantation continues for all islet transplant recipients. The data are confirmed via regularly scheduled site visits that include 100% data audit for adverse events. The reported data are coded for system/organ class and preferred term for tabulation and summary reporting, using the Medical Dictionary for Regulatory Activities, a part of the overall data quality and assurance process integral to The Emmes Corporation's Advantage EDC system. The coding is conducted by trained Emmes medical coders. Over the years of the Registry, both the MedDRA lexicon and coding processes, as well as the data structures for reporting adverse events have evolved. In the 11<sup>th</sup> Annual Report the entire history of serious adverse events has been re-coded to the current MedDRA lexicon (Version 19.0 or above), using a uniform process and the most complete descriptions of all the reported adverse events.

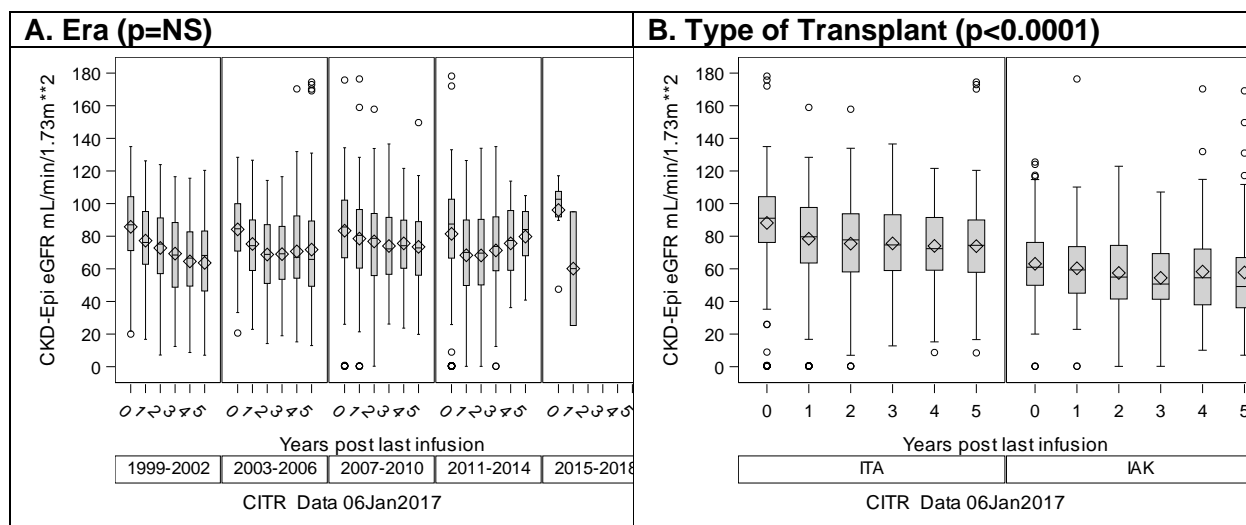
From the laboratory determinations, ALT and AST levels typically rise after islet transplantation, then level off, ALT remained elevated over 5 years post-last infusion in recipients who received induction immunosuppression with IL2A-alone while recipients who received other regimens gradually returned to baseline levels ( $p = 0.0002$ ). Also, ALT levels decreased over 5 years post-last infusion among recipients who received maintenance immunosuppression with CNI+IMPDH, but remained elevated among those who received other regimens ( $p = 0.0005$ ). Similar trends with respect to rise after islet transplantation and importance of immunosuppression regimens are observed for AST. AST was significantly higher in IAK than ITA ( $p = 0.008$ ).

Serum creatinine rose slightly but steadily over years of follow-up after initial islet transplant, in both ITA and IAK, but started higher in IAK. Those aged 35 and over also had higher initial levels. Recipients who received the fewest IEQ's infused showed the greatest increase ( $p = 0.0001$ ).

The decline in eGFR (CKD-Epi) after islet transplantation is both statistically significant and clinically important. IAK had much lower pre-transplant levels than ITA, which then declined at a slower rate (Exhibit 5B p<0.0001). Initial levels were also lower in recipients age 35 and older and declined at a slower rate compared to younger recipients. Levels were generally lower among recipients managed with CNI+IMPDH compared to other maintenance immunosuppression regimens (p=0.002).

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<sup>3</sup>, CITR allograft recipients had much lower mean eGFR (91±1SE for ITA and 62±2 for IAK) at their first transplant. CITR ITA recipients exhibited a decline in eGFR of 12 ml/min/1.73m<sup>3</sup> and IAK experienced a mean decline of 2 ml/min/1.73m<sup>3</sup> in 5 years from last infusion, compared to a mean decline of about 9 ml/min/1.73m<sup>3</sup> over the first 5 years in the DCCT.

**Exhibit 5  
Chronic Kidney Disease Collaboration (CKD-EPI) Estimated GFR (mL/min/1.73m<sup>2</sup>)**



**Neoplasms.** A total of 189 instances of neoplasm have been diagnosed in 101 of the 1,399 islet recipients who collectively represent a total of 7,963 person-years of observed follow-up. This equates to about 0.02 neoplasms per person-year. Of all neoplasms reported, 61% were deemed possibly related to immunosuppression, and 12% definitely related. The outcome of 69% of events was complete recovery with an additional 5% recovered with sequelae. There were 41 instances in 23 patients of basal carcinoma of the skin and 86 instances in 38 patients of squamous carcinoma of the skin. There were 56 instances in 39 recipients of non-skin cancers. The most common types of non-skin cancers reported were (# of cases): post-transplant lymphoproliferative (9), papillary (5), and ductal carcinoma (5).

**Deaths.** There have been 77 reports of death to the Registry for islet allograft recipients, for 5.5% crude mortality over a mean of 5.8 years elapsed follow-up per patient (including periods after complete graft failure and loss to observed follow-up). The most common causes of death were (# cases): cardiovascular (15), neoplasm (11), infection (including pneumonia) (9), hemorrhage (4), and complications of diabetes (3). Twenty-four deaths did not have a cause specified.

## CONCLUSIONS

The number of North American centers performing allogeneic islet transplantation, as well as the number allogeneic islet transplant recipients have fluctuated substantially over the life of the CITR, with the number of centers peaking in 2005 and then declining in 2006/2007. With the addition of Clinical Islet Transplantation (CIT) Consortium protocols from 2008 to 2015, the number of new islet cell recipients rebounded somewhat in North America from 2008 through 2012, but activity has since declined again. New allograft recipient activity at the Eurasian and Australian sites has paralleled the North American experience. In the US, a number of individual sites are currently pursuing licensure of allogeneic islet transplantation as a tissue product.

The safety-risk profile indicates that over 1999-2022, 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 group, which were very low to start.

The most remarkable clinical effect of islet transplantation are the very high levels of resolution of severe hypoglycemic events which are sustained long-term, even after complete loss of graft function (Exhibit 3, panels D1 and D2 – while the event rates for absence of severe hypoglycemic events (ASHE) are lower when C-peptide is <0.3 ng/mL, they are still at least 70%). The fundamental determinant of clinical benefit is maintenance of C-peptide ≥0.3 ng/mL: the higher, the better (Exhibit 3, all panels).

## Acknowledgments and Disclaimers

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Prepared by:

CITR Coordinating Center  
The Emmes Corporation, Rockville, MD  
[www.citregistry.org](http://www.citregistry.org)

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