A PHASE 3 SINGLE CENTER STUDY OF ISLET TRANSPLANTATION IN NON-UREMIC DIABETIC PATIENTS

Principal Investigator: Daniel Borja-Cacho, MD
Northwestern University
676 N. Saint Clair Street, Suite 1900
Chicago, IL 60611
Phone: (312) 695-6132
Fax: (866) 575-5440
daniel.borja-cacho@northwestern.edu

Sub-Investigators: Joseph Leventhal, MD, PhD
Northwestern University
Department of Surgery
Comprehensive Transplant Center

John Friedewald, MD
Northwestern University
Department of Surgery
Comprehensive Transplant Center

Nitin Katariya, MD
Northwestern University
Department of Surgery
Comprehensive Transplant Center

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Northwestern University
Comprehensive Transplant Center
Feinberg School of Medicine
676 N. Saint Clair Street, Suite 1900
Chicago, IL 60611

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List of Abbreviations

AE	Adverse event
BG	Blood glucose
BMI	Body mass index
BW	Body weight
CBC	Complete blood count
CFR	Code of federal regulations
cGCP	Current Good clinical practice
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CRF	Case report form
DIC	Disseminated intravascular coagulation
DSMB	Data safety monitoring board
EBV	Epstein barr virus
EDTA	Ethylenediaminetetraacetic acid
FDA	Food and drug administration
G-CSF	Granulocyte colony stimulating factor
GFR	Glomerular filtration rate
HbA1c	Glycosylated hemoglobin
HIV	Human immunodeficiency virus
HLA	Histocompatibility antigen
HSV	Herpes simplex virus
HTLV1	Human T-cell lymphotropic virus Type 1
ICH	International conference on harmonization
IE	Islet equivalents
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional review board
IV	Intravenous
LDL	Low-density lipoproteins
LFTs	Liver function tests
MMTT	Mixed-meal tolerance test
NOD	Non-obese diabetic
OPO	Organ Procurement Organization
PCR	Polymerase chain reaction
PI	Principal Investigator
PLT	Platelet count
PNF	Primary non-function
PRA	Panel reactive antibodies
PTLD	Post-transplant lymphoproliferative disorder
PT	Prothrombin time
PTT	Partial thromboplastin time
SAE	Serious adverse event
SC	Subcutaneous
SGOT	Serum glutamic-oxaloacetic transaminase

SGPT	Serum glutamate pyruvate transaminase
SOP	Standard operating procedure
TID	Type 1 diabetes
TB	Tuberculosis
TCAE	Terminology criteria for adverse events
TNF	Tumor necrosis factor
TNFR	Tumor necrosis factor receptor
ULN	Upper limit of normal
UNOS	United network for organ sharing
WHO	World health organization

Study Summary

Title	A phase 3 single center study of Islet Transplantation in Non-uremic Diabetic Patients
Short Title	Islet IND
Protocol Number	12.0
Phase	Clinical study phase 3
Methodology	Prospective, single arm, single center study in islet transplantation
Study Duration	Start of screening to 2 year post last subsequent transplant
Study Center(s)	Single-center
Objectives	To determine the proportion of subjects with a change in HbA1c, free of severe hypoglycemic events and proportion of insulin-independent subjects at two year after the final islet transplant
Number of Subjects	40 enrolled subjects, 18 transplanted subjects
Diagnosis and Main Inclusion Criteria	Non-uremic type 1 diabetics with hypoglycemia unawareness
Study Product, Dose, Route, Regimen	Allogeneic islet cells for transplantation via intraportal infusion
Duration of administration	Not to exceed more than 3 separate islet infusions
Reference therapy	Insulin
Statistical Methodology	Binomial test, Fisher's Exact Test or Chi-square test

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (GCP); (FDA Title 21, parts 45, 50, 56, and 312 and International Conference on Harmonization guidelines [ICH]), applicable government regulations and institutional research policies and procedures.

By signing below, I agree to conduct the research by US and International Standards of GCP FDA Title 21, parts 45, 50, 56, and 312 and ICH guidelines. Being the principal investigator (PI), I also agree to oversee that the sub-investigators and all research staff abide by the same standards and principles.

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Name Date

Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Type 1 diabetes (T1D) afflicts nearly 2 million people in the United States, most of them children or young adults(1). Untreated, it is a fatal disease. Exogenous insulin, administered by multiple injections or by a continuous subcutaneous (SC) infusion from a wearable pump, allow long term survival in those who develop the disease, and most who are treated in this way will have a very good health-related quality of life(2). However, insulin therapy does not provide normal glycemic control, and long term survivors commonly develop vascular complications such as diabetic retinopathy (the most common cause of adult blindness) and diabetic nephropathy (the most common indication for adult kidney transplantation)(3). The Diabetes Control and Complications Trial (DCCT) established that these microvascular complications of diabetes can be prevented by maintaining near-normal glucose control in patients with T1D(4). However, this degree of control is not always achievable despite modern insulin analogs and delivery systems(5), and when achieved, it is invariably associated with episodes of insulin-induced hypoglycemia that can be life-threatening(6). A small minority of individuals with T1D develop hypoglycemia unawareness, a condition that is life-threatening, is associated with severe deterioration in quality of life and activity restriction, and is not amenable to medical therapy (6, 7).

The hope of achieving near-normal glucose control without hypoglycemia in T1D has provided the impetus for developing effective strategies for β-cell replacement via pancreas or isolated islet transplantation. When successful, pancreas transplantation can normalize blood glucose (BG) in diabetic recipients, with associated stabilization and even reversal of microvascular complications(8). However, the risks of the procedure (an almost 10% early failure rate due to technical complications, anastomotic leak, bleeding, and infection) and the need for lifelong immunosuppression has in most centers limited the target population of this therapy to diabetics <50 years of age with minimal or no coronary artery disease, and at some centers pancreas transplant is offered only with concomitant kidney transplant(9). As a result, T1D patients in need of β-cell replacement are often excluded from whole pancreas transplantation. Islet transplantation, in contrast, is accomplished by a much simpler procedure in which the islets are infused into the portal vein(10). While this procedure is not without risk, the procedural morbidity is much less than that of whole pancreas transplantation(11).

On the other hand, whereas about 80% of whole pancreas transplant recipients will be insulin independent at one year after their transplant, <10% of 447 islet recipients transplanted between 1990 and 1999 achieved one year insulin independence (12). This was attributed to low engrafted islet mass combined with high metabolic demand imposed by glucocorticoids used to prevent rejection. In the year 2000, the group from Edmonton reported a series of 7 consecutive

islet transplant recipients treated with islets from multiple donors and a glucocorticoid-free immunosuppressive regimen (13). These islet recipients were insulin free at follow-up ranging from 4.5 to 15 months. All of the recipients had experienced severe hypoglycemic episodes prior to transplant, and afterwards, none did. The efficacy of the Edmonton approach has now been confirmed by several other centers, and represents a major breakthrough in the field (14). However, it has also become clear that, in most islet recipients, there is loss of graft function over time; in Edmonton, insulin-independence rates have declined from 72% at one year to 28% by three years(15). A multicenter trial using the Edmonton protocol has both confirmed the results of the initial experience and raised questions relating to the expansion of the procedure to multiple centers, the toxicities of the immunosuppressive regimen, and the evaluation of the islet product (14).

In 2006, the NIH initiated several multi-center (Clinical Islet Transplantation Consortium) clinical trials of islet transplantation with the primary goal of establishing islet transplantation as a therapeutic treatment option for patients with type 1 diabetes either already have had a successful kidney transplant or with severe hypoglycemic events and good native renal function. The clinical protocol utilized for these trials improved from the Edmonton protocol in that it incorporates (1) T cell depletion anti-thymocyte antibody(16, 17); (2) peri-transplant anti-inflammatory therapy using TNF-a blockade(16); (3) aggressive control of glucose homeostasis after transplant with continuing, albeit reduced, insulin therapy(18); (4) short-term anticoagulation therapy peri-intraportal islet infusion(18, 19).

Northwestern is one of the clinical centers of the Consortium and has successfully transplanted a total of eighteen patients with thirty-one islet preparations using this protocol in the past four and a half years. The current study protocol modifies the protocol of the CIT Consortium and substituted anti-thymocyte polyclonal antibody with alemtuzumab which has been shown to have efficacy in both pre-clinical model as well as clinical trials of allogeneic islet transplantation.

1.2 Investigational Agent

Human islets will be obtained from whole pancreases from adult human heart-beating cadaver donors through the organ procurement processes set forth by the United Network for Organ Sharing (UNOS), or its designated Organ Procurement Organizations (OPO). Criteria for organ donation will be those already in use for organ transplantation at Northwestern Memorial Hospital. The minimum donor recipient matching will be ABO compatibility and negative T-cell crossmatch according to the NIH methodology as determined in the Gift Of Hope laboratories. The goal of cadaver donor inclusion criteria is to provide an optimal islet harvest with minimal recipient risk. An ideal donor will have a favorable medical, sexual and social history, physical examination, and laboratory evaluation.

Relevant inclusion criteria will include:

1. Multi-organ donor
2. Adequate in-situ hypothermic perfusion
3. Maximum 12 hour cold ischemic time
4. Donor age 15-60 years
5. University of Wisconsin or HTK solution for perfusion and cold storage

Relevant exclusion criteria will include:

1. Pre-existing metabolic diseases, including diabetes mellitus type 1 or 2
2. Malignancies other than primary brain tumor
3. Septicemia
4. Hypotensive episodes only if significant biochemical abnormalities occur (this includes elevation of serum creatinine levels > 50% of the initial value or elevation of transaminases to levels greater than two times the upper limit of normal
5. Evidence of clinical or active viral Hepatitis A, B, or C
6. Acquired Immunodeficiency Syndrome (AIDS)
7. HIV seropositivity (HIV-I or HIV-II)
8. HTLV-III
9. Syphilis
10. Active viral encephalitis of unknown origin
11. Treated or active tuberculosis
12. Known high risk category such as intravenous drug use, incarceration, and high-risk sexual behavior within 5 years prior to time of death: men who have had sex with men, individuals who have engaged in prostitution, and individuals whose sexual partners have engaged in high-risk sexual behavior
13. Serious illness of unknown etiology (i.e. Persons whose history, physical exam, medical records, or autopsy reports reveal evidence of high-risk behavior such as needle track marks, unexplained weight loss or persistent lymphadenopathy)

Islet manufacturing will be performed in the Northwestern Memorial Hospital Good Manufacturing Practices facility on Olson 7th floor. Standard Operating Procedures developed for islet isolation for the CIT trials will be used for this study.

1.3 Preclinical Data

Data using alemtuzumab (Campath) as a cell-depleting induction therapy for islet cell transplantation has been mainly conducted in human subjects based on safety and efficacy data of using this agent in other types of organ transplantation (mainly kidney and pancreas transplantation). Data from human islet cell transplantation are summarized in Section 1.4.

1.4 Clinical Data to Date

To date, two clinical trials using alemtuzumab induction for allogeneic islet cell transplantation have been published. The first trial reported seven patients with type 1 diabetes and end-stage renal disease who underwent simultaneous allogeneic islet and kidney transplantation (20). Patients received alemtuzumab for induction immunosuppression, followed by sirolimus and tacrolimus. No glucocorticoids were given at any time. Four out of seven patients became insulin independent at 1 year, with the other three reduced insulin use to less than 25% of the pre-transplant requirement. The second trial reported three patients with unstable type 1 diabetes who underwent islet transplantation with alemtuzumab induction and sirolimus-tacrolimus maintenance for 3 months and then sirolimus-mycophenolic acid maintenance thereafter (21).

The authors reported superior long-term islet graft outcome in the alemtuzumab group compared with historical group using the Edmonton protocol. The administration of alemtuzumab was well tolerated and there was no increased incidence of infections in alemtuzumab subjects despite profound, prolonged lymphocyte depletion.

At the Comprehensive Transplant Center of Northwestern Memorial Hospital, alemtuzumab is the standard induction therapy for kidney and/or pancreas transplantation(22, 23), in addition to being the induction therapy for one of the two tolerance trial using donor stem cell infusions combined with kidney transplantation in HLA-identical donor-recipient pairs. Therefore, we have accumulated significant experiences of using this agent in our various transplantation populations and of managing any side effects and complications that might be associated with this induction agent.

1.5 Dose Rationale and Risk/Benefits

1.5.1

For dose of islets for infusion: minimum of 5,000 IEQ/kg of body weight for first infusion and minimum of 4,000 IEQ/kg of body weight for subsequent infusions. These islet dose guidelines have been used in the CIT Consortium trials and have been associated with 30-40% of insulin-independence after the first islet infusion and 100% of insulin-independence after the second islet infusion.

For alemtuzumab induction: a one-time 30mg i.v. on Day 0 will be given to all recipients in combination with appropriate pre-medications, 2 hours prior to the islet cell infusion. This dose is identical to that used in our organ recipients of kidney and/or pancreas allograft, and is consistent with published trials of islet transplantation described above.

The advantage of alemtuzumab as an induction immunosuppression agent is its tolerability and ease of administration (long half life, single dose administration).

1.5.2 Risks

Certain risks are associated with participation in this clinical trial. Although described in individual detail below, there are risks associated with transmission of disease from donor to recipient, microbial contamination of islet preparations, sensitization of the recipient to donor antigens, psychological impact of successful or failed islet transplantation, islet infusion procedure, use of immunosuppressive and protocol driven medications, and minimal risks associated with general procedures such as blood draws.

1.5.3 Transmission of disease from donor to recipient

Transplantation of human cadaveric islets is associated with risks equivalent to that in solid organ transplantation (24-26). Pancreatic islets will be isolated from donors that have been screened in accordance with standards set forth by the United Network for Organ Sharing (UNOS), or it's designated Organ Procurement Organization (OPO). A donor must have favorable medical, sexual, and social history with clear standard laboratory tests for low-risk of

transmission of donor disease. Their blood is screened for HIV, HTLV I/II, Hep B, Hep C, CMV, EBV and syphilis. Significant other and/or family members are questioned about high risk lifestyles and medical history. If pre-existing metabolic disease of the donor is uncovered this would exclude them from the donation process.

1.5.4 Microbial contamination of islet preparations

The process of isolating islets from the solid pancreas is an extensive technique and the risk of bacterial contamination does exist. Processed islets must meet lot release criteria before use in transplantation. A negative Gram stain and endotoxin determination must be completed prior to product release for transplantation. Broad spectrum antibiotics are added to the released product prior to transplantation and the recipient is given prophylactic antibiotic and anti-viral medication.

1.5.5 Sensitization of the recipient to donor antigens

Islet transplant recipients may become sensitized to donor histocompatibility antigens (HLA), causing the development of panel reactive alloantibodies (PRA). If this occurs it may delay or alter the recipient's ability to receive subsequent transplants.

1.5.6 Psychological impact of successful or failed islet transplantation

The potential of psychological disappointment progressing to clinical depression exists if failure to reverse hyperglycemia and the inability to maintain insulin independence occur.

1.5.7 Islet infusion procedure

The following potential risks have been identified with islet cell transplantation: moderate pain or discomfort; bleeding from a puncture to the liver; damage to the liver or blood vessels in the abdomen; damage to the gallbladder; bleeding from use of anti-coagulants; portal vein thrombosis; apnea; and pleural effusion.

1.5.8 Immunosuppressive and protocol driven medications

Alemtuzumab (Campath-1H) Events include rigors, fever, nausea/vomiting, fatigue, hypotension, shortness of breath, bronchospasm, chills, pruritus, headache, diarrhea, urticria, infection and cancer.

Basiliximab (Simulect) Events include constipation, nausea, abdominal pain, vomiting, diarrhea, dyspepsia, peripheral edema, fever, viral infections, hyperkalemia, hypokalemia, hyperglycemia, hypercholesterolemia, hypophosphatemia, hyperuricemia, urinary tract infections, upper respiratory infections, surgical wound complications, acne, hypertension, headache, tremor, insomnia, and anemia.

Sirolimus (Rapamune) Events include hypercholesterolemia, hyperlipemia, rash, arthralgia, diarrhea, anemia, leucopenia, thrombocytopenia, and hypokalemia.

Tacrolimus (Prograf) Events include hypertension, diabetes, nephrotoxicity, hyperkalemia, dyslipidemia, pruritus, neurotoxicity, neurologic sequelae, posterior reversible encephalopathy

syndrome, progressive multifocal leukoencephalopathy, interstitial lung disease, BK nephropathy, nausea, vomiting, and diarrhea.

Mycophenolate mofetil (Cellcept) and Mycophenolate sodium (Myfortic) Events include diarrhea, leucopenia, vomiting, infection, lymphoprolifertive disease, lymphomas, malignancies, multifocal leukoencephalopathy, pure red cell aplasia, and fetal harm if administered to pregnant woman.

Etanercept (Enbrel) Events include injection site reactions (erythema, pruritus, pain or swelling).

Enoxaparin (Lovenox) Events include bleeding, anemia, fever, and thrombocytopenia.

Pentoxifylline (Trental) Events include dyspepsia, nausea, vomiting, headache, and dizziness.

Valganciclovir (Valcyte) Events include leucopenia, fever, thrombus, and anorexia.

Valaciclovir (Valtrex) Events include confusion, agitation, depression, weakness, headache, nausea, vomiting, diarrhea, stomach pain, dizziness, rash, hives, changes in urination and problems with coordination.

Trimethoprim/Sulfamethoxazole (SeptraSS/Bactrim) Events include leucopenia, thrombocytopenia, anemia, fever, chills, vertigo, seizures, meningitis, depression, anorexia, nausea, vomiting, liver damage, large bowel inflammation, rash, and hives.

Atovaquone (Mepron) (substituted for Bactrim) Events include nausea, diarrhea, constipation, headache, insomnia, diaphoresis, dizziness, drowsiness, dysgeusia.

Clotrimazole (Mycelex troche) Events include nausea, vomiting, and diarrhea.

Nystatin (substituted for Mycelex troche) events include nausea, diarrhea, and vomiting.

1.5.9 Blood draw

Events include pain, bruising, fainting, infection, swelling, or a small blood clot.

1.5.10 Benefits

There may be no direct medical benefit for subjects participating in this study. The knowledge gained from these studies may help the researchers develop a safer and more effective treatment for type 1 diabetes that could help patients obtain better glucose control and reduce the risks of diabetes-related complications such as heart and kidney disease.

2 Study Objectives

Primary Objective: To demonstrate the safety and efficacy of islet transplantation under alemtuzumab induction for treatment of TID in subjects with hypoglycemia unawareness and a history of severe hypoglycemic episodes.

Secondary Objective: To relate clinical transplant outcomes based upon islet quantity/quality to organ donor characteristics.

3 Study Design

3.1 General Design

- Phase 3, prospective, single arm single center study of islet cell transplantation
- Identify and approach potential study subjects
    - Obtain written informed consent on potential study subjects who agree to participate
    - Perform screening assessments and evaluate all inclusion/exclusion criteria to determine subject eligibility
    - Place eligible subject on transplant waiting list
    - Islet preparation using compatible donor organ available
    - Subject will receive immunosuppressive regimen, initial islet transplant and subsequent islet transplants if indicated
- Subjects will be followed up for two year post last transplant and may receive up to a total of 3 islet transplants.

3.2 Primary Study Endpoints

To assess the efficacy of islet cell transplantation under alemtuzumab induction immunosuppression on the proportion of subjects with a change in HbA1c and free of severe hypoglycemic events through two years after the final islet transplant.

3.3 Secondary Study Endpoints

- To assess the proportion of insulin-independent subjects at *two years* after the final islet transplant.
- To compare islet graft outcome between alemtuzumab induction and historical anti-thymocyte induction groups.
- To relate clinical transplant outcomes based upon islet quantity/quality to organ donor characteristics.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Male and female patients age 18-65 years of age at consent
2. Ability to provide written informed consent
3. Mentally stable and able to comply with the procedures of the study protocol
4. Patients with T1D and insulin-dependent for at least 5 years fulfilling the following criteria:
    a. Absent stimulated c-peptide (<0.3 ng/mL) in response to a mixed meal tolerance test (MMTT; ensure 6 mL/kg body weight to a maximum of 360mL) measured at 60 and 90 min after the start of consumption
    b. Patients who have been followed by a qualified physician for diabetes management for a minimum of 12 months

   c. At least one episode of severe hypoglycemia in the past 12 months
   d. A Clarke score of 4 or more defining reduced awareness of hypoglycemia
5. Or, previous islet cell transplant recipients who have returned to partial or full insulin usage and are taking maintenance immunosuppression medications.

4.2 Exclusion Criteria

1. Body mass index (BMI) > 30
2. Insulin requirement of > 1.0 IU/kg/day
3. HbA1c > 10%
4. Calculated glomerular filtration rate (GFR) < 80mL/min for transplant-naïve patients (using subjects serum creatinine and the Chronic Kidney Disease Epidemiology Collaboration equation CKD-EPI) or 50mL/min for previously transplanted patients currently on immunosuppression
5. Macroalbuminuria >300 mg/g creatinine
6. Panel reactive anti-HLA antibodies> 50% by flow cytometry
7. For female subjects: positive pregnancy test, breast feeding or unwillingness to use effective contraceptive measures for the duration of the study.
8. Active infection including hepatitis B, hepatitis C, HIV, or tuberculosis (TB)
9. Negative Epstein-Barr Virus (EBV) by IgG
10. Any history of malignancy except resected squamous or basal cell carcinoma
11. Alcohol or substance abuse
12. Baseline Hb below the lower limit of normal
13. International normalized ratio >1.5 and long term anticoagulant therapy
14. Clinically significant coronary artery disease
15. Elevated liver function tests >1.5 times upper limit of normal
16. Symptomatic cholecystolithiasis
17. Gastrointestinal disorders interfering with ability to absorb oral medications
18. Uncontrolled hyperlipidemia (LDL cholesterol >130 mg/dL and/or triglycerides >200 mg/dL)
19. Chronic corticosteroid use

4.3 Subject Recruitment and Screening

Subjects will be self-referred or referred by physicians.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects will be withdrawn from the study for the following reasons:

1. The subject withdraws consent to participate in the study
2. The subject is unwilling or unable to comply with the protocol
3. At the discretion of the investigator for medical reasons

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Even though subjects may be withdrawn prematurely from the study, we will continue to collect at least survival data on such subjects throughout the protocol defined follow-up period for that individual (though careful thought will be given to the full data set that should be collected on such individuals to fully support the analysis). Such data is important to the integrity of the final study analysis since early withdrawal could be related to the safety profile of the infused islets. If a subject withdraws consent to participate in the study, attempts will be made to obtain permission to record at least survival data up to the protocol-described end of subject follow-up period. We will also note what methods are used to contact such individuals before considering that these subjects are truly lost to follow-up (e.g. number of phone calls to subject, phone calls to next-of-kin if possible, certified letters, etc.).

5 Study Drug

5.1 Description

The final product of allogeneic islets will be in 200 mL sterile suspension of ≥70% viable, ≥30% pure, allogeneic human purified islets.

5.2 Treatment Regimen

The final product is supplied in up to three 200 mL bags, containing a dose of ≥5,000 IEQ/kg recipient body weight for the first transplant, and ≥4,000 IEQ/kg recipient body weight for subsequent transplants for administration by intraportal infusion.

5.3 Method for Assigning Subject ID Numbers

As subjects are consented they will be given a subject ID number sequentially.

5.4 Preparation and Administration of Study Drug

Islet manufacturing

The donor pancreas will be procured utilizing the usual techniques for whole-organ pancreas procurement and will be stored in UW or HTK solution. All whole-organ human pancreata will be procured, packaged and shipped according to standard United Network for Organ Sharing (UNOS) guidelines, Policy 5.0 Standard Packaging of Human Organ and Tissue Typing Materials, Sections 5.1-5.6. The pancreas will be transferred to our islet manufacturing facility located in the Olson Pavilion of Northwestern Memorial Hospital (refer to attached document: Northwestern Memorial Hospital Cell Therapy Processing Facility) for processing. The pancreas will be processed and the islets isolated utilizing premium grade of collagenase intraductal distention and digestion technique. All solutions utilized for isolation of the islets will contain antibiotics including gentamycin, penicillin and amphotericin B. If patients have a history of severe allergy to Penicillin (anaphylaxis), Penicillin will be excluded from the antibiotics used to sterilize the islet product. The final islet product will be washed free of antibiotics prior to sterility testing. Quantification of islet tissue will be conducted with dithizone staining of islets and quantification with size discrimination. Islet quantity will be defined in terms of a standard 150μ size and expressed as islet equivalents. The mass of islets isolated are anticipated to be approximately 300-800,000 in a volume of approximately 4-8 cc of acinar and islet tissue. The

viability of the islets will be ascertained by in vitro glucose stimulation and assay of insulin release (19). Samples of islet tissue will be submitted to the hospital clinical microbiology lab and analyzed for gram stain, microbial content and antibiotic sensitivity. The gram stain results will be obtained prior to final product release. This will be performed in the microbiology lab at Northwestern Memorial Hospital. This will be performed on a STAT status. If gram stain results are positive, the procedure will not proceed. Aerobic, anaerobic and fungal cultures of the final islet product are also sent to the microbiology laboratory for analysis and results are obtained following transplantation. An identification of the organism and antibiotic sensitivity will be obtained. Perioperative antibiotics will be continued until final results are obtained. Based on the results, we will determine if a change in antibiotic therapy is required. As a control for residual antibiotics, a bioassay will be performed using a sample of liquid from the final islet product. Following completion of the islet isolation, the pancreatic islets may be kept in culture for up to 72 hours at Northwestern. The islets will be evaluated for sterility, viability, and potency.

The final preparation of the pancreatic islet allografts will be undertaken in the Northwestern Islet Isolation Facility. Prior to transplantation at Northwestern Memorial Hospital, gram stain, endotoxin testing, and propidium iodide staining will assure pancreatic islet sterility and viability. Islet aliquots will also be set up for culture and glucose challenge. When all these conditions are met, the islets will be transplanted.

The islet preparation consisting of a packed tissue volume of less than 10 ml is dispersed in approximately 200 ml of transplantation medium containing 25% human albumin and heparin and infused under sterile conditions over 20-30 minutes by gravity drainage in a percutaneous catheter passed into the portal vein under fluoroscopic guidance. A Gelfoam plug or embolectomy coil will be placed into the peripheral catheter tract as the catheter is withdrawn to reduce the chance of bleeding. The transplant will occur in Interventional Radiology with appropriate standard operating procedures and monitoring or in the operating room if cannulation can't be obtained.

The following criteria will be used to determine adequacy of the isolation:

a) Yield of at least 5,000 (or 4,000 if subsequent islet infusions) islet equivalents/kg of body weight
b) Minimum viability acceptance level of 70%
c) Endotoxin limit of 5 EU/kg/3ml/kg = 1.7 EU/ml (a typical islet product has a maximum human dose of 3 ml/kg. The endotoxin limit is calculated as follows: [5EU/kg] / [total volume of product / patient mass in kg] = EU/ml product [max. allowed EU level]). The endotoxin test is prospective. The final islet product will not be released until results are obtained and under the specified limit.

Islet transplantation

Transplantation will occur after the isolation is complete with at least 5,000 (or 4,000 if subsequent islet infusions) islet equivalents/kg of recipient body weight. Prior to transplantation,

it will be established that the recipient is ABO compatible with the donor; the donor's serology tests (except CMV) have been obtained; the recipient's admission screening tests are satisfactory; and the patient has received pre-transplantation medications. Insertion into the portal vein of a percutaneous transhepatic catheter is completed in the radiology department under conscious sedation. Alternatively, access to a mesenteric or omental venous tributary of the portal vein can be obtained by mini-laparotomy under general anesthesia if percutaneous access cannot be achieved. The islet cells (packed tissue volume of less than 10 ml dispersed in approximately 200 ml of transplant media) are infused through IV tubing into the portal vein, by gravity infusion, in approximately 30 minutes per bag. Portal venous pressure is measured before the islet infusion, in between bags if applicable and after the infusion. The guidelines for portal venous pressure monitoring and maintenance during the islet infusion are as follows: if the initial portal pressure (PI) is ≤ 20 mmHg start infusion; if PI rises above 22 mmHg, infusion should be held for 10 minutes, if PI falls below 18 mmHg the infusion may continue, if not, infusion should be terminated; if there is a change in absolute portal pressure that exceeds more than double the baseline recording and the reading is between 15-21 mmHg the infusion should be held for 10 minutes, if after that time the portal pressure is less than 18 mmHg continue, if the pressure remains greater than 18 mmHg or is more than 15 mmHg and greater than twice the initial pressure, the infusion should be terminated; if there is a change in absolute portal pressure that exceeds more than double the initial recording and the reading is less than 15 mmHg the infusion can continue. Subsequent bags should only be infused if the portal pressure remains below 18 mmHg and less than twice the initial portal pressure. The catheter is removed and the small insertion site is bandaged. The islet cells produce insulin immediately and the patient's blood glucose is closely monitored. Changes in the patient's insulin dosage are made hourly for several hours, before each meal and at bedtime. Anti-infective prophylaxis will begin within 4 hours of transplantation to include: Ceftriaxone 1 gm IV (if not penicillin allergic) with a follow-up dose in 12 hours or Aztreonam 1 gm IV (if penicillin allergic) with a follow-up dose in 8 hours, Bactrim SS one tablet P.O. daily beginning day 1 post-transplant (or Mepron if Bactrim allergic) will be given for pneumocystis pneumonia prophylaxis and continued for a minimum of one year post-transplantation. CMV negative patients who receive islets from CMV negative donors will receive Valaciclovir prophylaxis 500mg P.O. QD from day of transplant through six months post transplant. Any other combination of CMV status the recipient will receive Valganciclovir prophylaxis 450mg P.O QD or its equivalent for three months post-transplant.

We will not ship islets from our processing facility to other clinical sites within or outside the City of Chicago. Expiration date of the final product will be established as 6 hours from placement of the final product into the final product bag.

5.5 Subject Compliance Monitoring

Post transplant the subject will be given a schedule for the follow up period and tentative dates. It will be the subject's responsibility to contact the coordinator with any cancellations or need to reschedule. If the subject does not come in for a study visit they will be contacted that day. If they are lost to follow up phone calls and certified letters will be sent to determine the cause for lack of study follow visits.

5.6 Prior and Concomitant Therapy

- Prior and/or concomitant medical therapy will be collected from screening to study completion, i.e. two year from final islet transplant.
- Chronic use of systemic steroids except ≥5 mg prednisone daily, or an equivalent dose of hydrocortisone is not permitted during the study. Alternative therapies will be discussed with patients and physicians caring for patients for indicated conditions.

5.7 Packaging

- Packaging of the islets is described in detail in Section 5.4.

5.8 Receiving, Storage, Dispensing and Return

5.8.1 Receipt of Drug Supplies

Islet preparations appropriately packaged will be transported from The Mathews Center for Cellular Therapy to Feinberg Interventional Radiology Suite (4th floor) in sterile infusion bags. Upon receipt of islets, the integrity of infusion bags and islet products will be inspected by the PI, and product release forms will be signed by the PI if product is deemed appropriate for infusion.

5.8.2 Storage

The islet product will be placed in culture for at least 36 hours but no longer than 72 hours prior to transplantation. Islet product will not be stored and will be infused in less than 6 hours after it is finally packaged.

5.8.3 Dispensing of Study Drug

Islet product dispensing to a given individual is based on ABO compatibility, UNOS wait time, final cross-match, and final islet yield, much like transplantation of solid organs (kidney, pancreas, lung, small bowels). The details are described as in Section 5.4.

5.8.4 Return or Destruction of Study Drug

If an islet product is not infused into the intended recipient, the product will be destroyed as biohazards using appropriate methods.

6 Study Procedures

6.1 Pre-Screening

Subjects will be self-referred or referred by physicians. Potential subjects will be consented using the study consent form. For the sake of subject convenience, this consent may occur over the phone. Subjects will be sent a copy of the consent form, given adequate time to read the form and discuss with study staff prior to signing.

After signing the consent form, the subjects will be asked to complete a screening questionnaire to determine whether they meet basic eligibility for the study. If they appear basically eligible, the study team will perform a confirmatory medical record review. If the subject appears eligible after medical record review, they will be invited on site for screening assessments.

6.2 Screening Visit (Visit 1 - In Person Screening)

Subjects will be re-consented at Visit 1 if the previous consent took place over the phone.

The following will be performed at the screening visit unless assessment has been performed within the designated timeframe:

Allowable Timeframe prior to the date of Enrollment	Screening assessments
No Limit	EBV IgG (positive result required for eligibility); Blood type (results on two separate dates required); HLA; Fasting & Stimulated c-peptide (or MMTT), Abdominal US; Quantiferon Gold TB
Within 6 months	CBC; Chemistry; Lipids; PRA; Pregnancy test (females)
Within 1 year	Retinopathy evaluation; Physical Exam; CXR; ECG; TSH; Serology; Coagulation; Mammogram (female > 40 years), Pap smear; CMV IgG/IgM (if negative); HbA1c; PSA (if male > 50 years or history of benign prostate hypertrophy); first morning spot urine; calculated GFR
Within 2 years	Cardiac stress test or Angiogram
Within 10 years	Colorectal cancer screening (up to date, if > 50 years old)

Any previously completed cardiac test procedures will be reviewed for significant coronary artery disease. Additional testing will be performed as clinically indicated. Subjects with recent cardiac symptoms (≤ 6 months) consistent with CAD will be excluded until further evaluation has been completed.

Serology will include Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis B core antibody, Hepatitis C antibody, HIV, HTLV and RPR.

A first morning spot urine will be collected for protein and creatinine.

A calculated GFR will be determined utilizing the subject's measured serum creatinine and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Fasting and stimulated serum glucose/c-peptides will be determined by utilizing an Ensure mixed meal tolerance test (MMTT). The fasting blood draw will be followed by ingestion of ensure of 6 mL per kg body weight (to a maximum of 360 mL) over a 5 minute period of time and serum determination of c-peptide at 60 and 90 minutes. Subjects eligible for participation must have documented lack of c-peptide response.

In addition to the protocol required screening assessments, subjects should meet transplant site-specific requirements for transplant.

6.2.1 Waiting List/Baseline (Visit 2)

After completion of the screening assessments, eligibility will be confirmed, and the subject will be enrolled into the study. Shortly after, they will be listed for an islet cell transplant through the United Network for Organ Sharing (UNOS). During the period when subjects are awaiting their first transplant, various assessments will need to be repeated in order to confirm continued eligibility. The Gift of Hope, the local organ procurement organization, will also require monthly blood samples to be sent in to their location to be stored for potential future crossmatch. See schedule of events for required timeframes for individual repeat assessments. As in any other transplant situation, medical conditions that arise (e.g., new serious infection, malignancy, compliance issues, etc.) may automatically trigger a re-evaluation of some assessments in order to determine whether the subject remains qualified. Only qualified subjects may proceed to donor organ matching and transplant. Ultimately, it will be the physician's discretion to proceed with crossmatch, should some assessments fall out of window. All out-of-window assessments in this case, should be repeated at baseline/hospital admit.

All one-time baseline assessments should be performed at hospital admit, and the results of these assessments will not affect the subject's eligibility for transplant.

6.2 In-patient hospitalization and transplant

Once a compatible islet preparation becomes available, subject eligibility will be re-confirmed. Subjects will be admitted to NMH for the transplant and will remain an inpatient for

approximately 3 days. Upon arrival, an H&P will be performed, STAT laboratory studies, ECG, and a CXR. Medication regime prior to allogeneic islet transplant will be initiated pending above results. Subject will receive immunosuppressive therapy and associated pre-medication prior to the islet cell transplant on Day 0.

If the subject does not become insulin independent three months post the first transplant they will be eligible for subsequent (2^{nd} or 3^{rd}) transplants. They will be admitted into NMH for the transplant and will receive Campath or Basiliximab as the induction immunosuppressant medication (dependent upon absolute lymphocyte count at time of transplant). Upon arrival the same testing will occur prior to transplant.

If subject clinically requires multiple transplants, rituximab may be used at the time of repeat transplant at a dose of $375mg/m^2$ the discretion of the Principle Investigator based on shared HLA antigens between subsequent donors with the first donor, as well as results from continuing monitoring of recipient ant-HLA antibodies.

6.2.2 Immunosuppressive medications

Alemtuzumab (Campath 1H) 30mg will be given as an IV infusion over 3 hours and premedication of 250mg methylprednisolone will be administered one hour prior to medication administration by IVP on Day 0 prior to initial islet transplant, and 2^{nd} or 3^{rd} transplants, dependent upon absolute lymphocyte count.

Basiliximab (Simulect) 20 mg will be given as an IV infusion over 20-30 minutes for 2nd or 3rd islet transplants approximately 2 hours prior to islet infusion and dose repeated on Day 4, only if absolute lymphocyte count is diminished to less than 5% of baseline.

*Tacrolimus (Prograf) will be administered at an initial dose of 2 mg PO BID on Day +1 and +2, and will be adjusted to the whole blood 12-hour trough with a therapeutic range of 10-12 ng/mL for the first 3 months, 8-10 ng/mL from 3-6 months, and 6-8 ng/mL thereafter.*Mycophenolate Mofetil (Cellcept) will be administered at an initial dose of 1000 mg PO BID on day 0, and will be maintained at a dose between 500-1500 mg PO BID thereafter.

*Mycophenolate Sodium (Myfortic) will be used at a dose between 360-900 mg PO BID as a replacement for mycophenolate mofetil.

*Sirolimus (Rapamune) Will be administered at an initial dose of 0.1mg/kg PO on Day 0 (day of transplant), followed by 0.05 mg/kg on Day 1. The daily dose will be adjusted to the whole blood 24 hour trough with a therapeutic range of 10-15 ng/mL for the first 3 months and 8-12 ng/mL thereafter.

*It will be up to the principle investigator's discretion to choose the combination of immunosuppression therapy that best suits each subject.

Rituximab (Rituxin) will be administered at the dose of 375mg/m^2 intravenously, at the discretion of the investigator for patients getting multiple transplants that have DSA. This medication will be administered at the time of the second and/or third transplant.

6.2.3 Concomitant Medications

Immunosuppressive/Anti-Inflammatory Therapy

Etanercept (Enbrel) will be administered at a dose of 50 mg IV over 30 minutes on Day 0 (1 hour prior to transplant) and 25 mg SC on Days +3, +7, +10.

Antibacterial, Antifungal, and Antiviral Prophylaxis

Broad spectrum antimicrobial prophylaxis will be administered preoperatively: Ceftriaxone 1 gm IV (if not penicillin allergic) with a follow-up dose in 12 hours or Aztreonam 1 gm IV (if penicillin allergic) with a follow-up dose in 8 hours

Trimethoprim/Sulfamethoxazole (Septra SS/Bactrim) will be administered at a dose of 80g/400mg PO QD starting on Day +1 for the duration of one year after the final transplant. If subject has sulfa allergies or is unable to tolerate this drug, Atovaquone (Mepron) 1500mg/10mL PO QD will be given as an alternative.

Clotrimazole (Mycelex Troche) will be administered as 1 PO QID starting on Day 0 and to be continued for 3 months after transplantation. If subject can't tolerate alternative antifungal medication can be substituted.

Valganciclovir (Valcyte) will be administered on Day 0 at a dose of 450 mg PO QD, increasing as tolerated to 900 mg QD on Day 12 and continue for 14 weeks post-transplant. If the CMV status of the donor and recipient are both negative administration will be replaced with valacyclovir..

Valacyclovir (Valtrex) will be administered on Day 0 post transplant at a dose of 500 mg PO QD for 6 months if CMV D-/R-..

Anticoagulation Prophylaxis/Hematological Agents

Heparin will be administered at a dose of 70 U/kg body weight of the recipient and divided equally among the islet bags given with the islet infusion. Post the transplant heparin will be given at a dose of 3 U/kg/hr via IV for the next 6 hours, then from hour 6 through hour 48 will be titrated based on dosing weight at admission to achieve and maintain PTT between 63-91 seconds, and for excursions outside of this range, adjust dosing per NMH policy CCP 07.0006 version 1.4, page 4 of 5

Enoxaparin (Lovenox) will be administered at a dose of 30 mg SC BID day 2 through Day 7 post islet transplant with first dose given 6 hours after heparin has been discontinued. Dose can be modified at the discretion of the PI.

Aspirin, enteric coated will be administered at a dose of 81 mg PO qPM starting 24 hours post transplant.

Pentoxifylline will be administered at a dose of 400 mg slow release TID starting on Day 0 prior to transplant and continued through Day 7 post transplant.

6.3 Follow up visits

Subject will undergo 24 month follow-up period following their last islet transplant. Refer to Schedule of Events (attachments) for clinical time point of specific follow-up procedures. If subjects are unable to achieve insulin independence at 3 months post- transplant subsequent transplants can be performed. The follow-up time points will reset with each subsequent transplant. If the time between transplants exceeds 24 months, the subject will be asked to continue monthly lab draws until the subsequent transplant occurs, at which point the 24 month follow up as outlined by the protocol would reset.

During the entire follow up period, we will communicate with the patient on a monthly basis (e.g. email communications) regarding other physicians and health care providers that the patient may have seen in the preceding month. If the patient has seen other physicians and health care providers in the preceding month, we may obtain their contact information and communicate with them directly regarding patient's transplantation and medications, particularly immunosuppressive drugs. If the patient is prescribed with any new medications by these other physicians or health care providers, we will perform pharmacological analysis to ensure that if drug-drug interactions are present, they are noted and appropriate actions are taken to ensure adequate dosing/levels of the anti-rejection medications.

7 Statistical Plan

7.1 Sample Size Determination

A total of 40 patients will be enrolled into the study in order to account for screen failures. We plan the sample size to be 18 subjects who will actually complete the study from enrollment to the end of participation. This sample size is comparable to that of subjects already enrolled in the CIT Consortium study, to which this group will be compared with.

7.2 Statistical Methods

There is no prior information on the standard error and effect of the rate of the favorable outcome variable since the study in this protocol is a pilot trial study using alemtuzumab as the induction agent for allogeneic islet cell transplantation. As such, it is not possible to estimate the sample size of this study at the start. However, given the rationale above, it is expected the patient outcome will be at least as good as those of NIH-funded Clinical Islet Transplant (CIT) study in which NMH is a participating center. Therefore it is not unreasonable to set the same sample size of 18 (the number of subjects NMH has enrolled for the CIT study) as the sample size requirement for this protocol. As the study proceeds and data accumulate, we will be able to revise the sample size estimates with the incoming data.

The analyses of this study will focus on the rate of favorable outcomes. The primary aim of the analysis is to assess if the proposed study is better than the CIT study at primary endpoint. The observed rate will be used as the point estimate of this study. Due to the limited sample sizes and potential low values in a 2X2 contingency table, the analysis will use one-side Fisher's Exact Test to test the hypothesis that the proposed study will have a significantly higher rate of favorable outcome than the CIT study. Alternatively, a one-sided binomial test statistics can be computed to compare the proportions of favorable outcome rates, followed by the p-value calculation with Monte Carlo simulation. The analyses at key secondary endpoints will be performed with the same statistical approaches. To account for the multiplicity of the key secondary tests, Benjamini and Hochberg's false discovery rate will be computed to identify the secondary endpoints at which the true rate of favorable outcome is greater than that of the CIT study.

In addition, summary descriptive statistics for baseline and demographic characteristics of patients will be computed and compared. Demographic data will include age, race, sex, etc. Data on a continuous scale will be summarized descriptively with mean, standard deviation, median and range, and compared to the patient cohort in the CIT study using a t-test. Categorical data will be presented as enumerations and percentages, and may be further compared to the patient cohort in the CIT study with two sample binomial test, Fisher's Exact Test or Chi-square test.

Statistics analysis will be conducted by Dr. Chunfa Jie from the Bioinformatics Division of the NU Genomics Core Facility.

7.3 Subject Population(s) for Analysis

- <u>All transplanted population</u>: Any subject transplanted with at least one islet infusion, regardless of compliance or reaching primary or secondary end points;

- Protocol-compliant population: Any subject was transplanted with at least one islet infusion and who was compliant with study protocol and reached primary and secondary study end points.

8 Safety and Adverse Events

8.1 Definitions

Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

All adverse events (including serious and unexpected adverse events) will be graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, published May 28, 2009 (v4.03: June 14, 2010).

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- death
- life-threatening event that places the subject at immediate risk of death
- initial inpatient hospitalization or prolongation of existing hospitalization
- persistent or significant disability
- congenital anomaly or birth defect
- event that required intervention to prevent permanent impairment or damage

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

Grading and Attribution

The severity of AE's experienced by the study subjects according to the criteria set forth in the CTCAE will be graded. AE severity will be graded on a scale from 1 to 5 according to the following standards in the CTCAE manual:

Grade 1 = mild AE
Grade 2 = moderate AE
Grade 3 = severe and undesirable AE
Grade 4 = life-threatening or disabling AE
Grade 5 = death

AE's not included in the CTCAE listing will be recorded and their severity graded from 1 to 5 according to the general grade definition provided below:

Grade 1	Mild	Transient or mild discomforts (< 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain).
Grade 2	Moderate	Mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible
Grade 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required hospitalization possible
Grade 4	Life-threatening	Extreme limitation in activity, significant assistance required; significant medical/therapy intervention required hospitalization or hospice care probable
Grade 5	Death	Death

Attribution will only be determined and collected for serious adverse events. The investigator will determine the relatedness of an AE to islet transplantation, which includes the transplant procedure and/or islet product, or to the immunosuppression and/or infection prophylaxis. The relationship will be defined by using the descriptors provided below:

Code	Descriptor	Definition
1	Unrelated	The AE is clearly not related
2	Unlikely	The AE is doubtfully related
3	Possible	The AE may be related
4	Probable	The AE is likely related
5	Definite	The AE is clearly related

Adverse Event Reporting Period

The study period during which adverse events must be reported will begin at the time of the in-person screening visit (Visit 1) and end 24 months after the participant's last islet infusion.

Please note that between visit 1 (in person screening) and visit 3 (Islet transplantation) only those adverse events that are related to study procedures (Screening/ Waitlist procedures) will be recorded. Once the participant receives the islet transplantation, all adverse events, regardless of relation, will be recorded.

When an Investigator identifies a serious adverse event (as defined above), the Investigator must notify the NU IRB and/or other Reporting Centers (the NUCRU, FDA and DSMB) of the serious adverse event within 24 hours of discovery.

Three possible reporting scenarios (to the appropriate health authorities) could arise after assessment of the event:

- No requirement to report. This would occur if the adverse event is deemed not serious by protocol definition.

- Standard reporting is required (report in IND annual report). This would occur if the adverse event were classified as one of the following: (a) serious, expected and drug related; (b) serious, expected and not drug related; or (c) serious, unexpected and not drug related.

- Expedited reporting is required. This would occur if the adverse event is considered serious, unexpected and drug related. These events must be reported by the Sponsor to the appropriate health authorities within 15 days unless the event is fatal or life-threatening; the latter must be reported within 7 days.

The PI, in any event, must report the serious adverse event to the NU IRB as mandated by the NU IRB.

Reporting Serious Adverse Events to the Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be provided listing of all SAE's on an ongoing basis. Further, the DSMB will be informed of expedited SAE's at the same time as regulatory authorities.

Pregnancy (SAE Reporting Requirements):
Any pregnancy that occurs during a clinical study with an investigational drug must be reported as an SAE for tracking purposes only. All pregnancies that are identified during this study need to be followed to conclusion and the outcome reported. Female participants should immediately inform the Investigator of any pregnancies and should be instructed by the Investigator to stop taking any study medication. The Investigator should report all pregnancies within 24 hours (as described above in SAE Reporting). The Investigator should counsel the participants and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the participants should continue until the conclusion of the pregnancy, and a follow-up SAE Reporting Form should be submitted detailing the outcome.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events will be followed by PI until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the PI will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. Death, adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study such as the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study will be recorded.

Abnormal Laboratory Values
A clinical laboratory abnormality will be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study (i.e. islet transplantation).
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study (i.e. diabetes), unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the research team will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded in the source document, and also in the appropriate adverse event case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period (see section 8.1) will be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events

8.3.1 Study Sponsor Notification by Investigator

In this study, the Study Sponsor is the PI of the study. A serious adverse event must be documented within 24 hours of the event. A Serious Adverse Event (SAE) form will be completed by the investigator. The investigator will keep a copy of this SAE form on file. Serious adverse events will be recorded and filed by:

Daniel Borja-Cacho, MD 312-695-6132 (p) or 866-575-5440 (f)

At the time of the initial report, the following information should be provided:

- Study identifier
- Subject number
- A description of the event
- Date of onset
- Current status
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following 48 hours, the investigator will document further information on the serious adverse event in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor.

8.3.2 EC/IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) will be submitted to the EC/IRB within 10 working days. Copies of each report and documentation of EC/IRB

notification and receipt will be kept in the Clinical Investigator's binder. Subject deaths will be reported within 24 hours.

8.3.3 FDA Notification by Sponsor

The PI shall notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with islet transplantation as soon as possible but no later than 7 calendar days from the original date of the event.

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the PI will submit the adverse event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

8.4 Stopping Rules

The study will be stopped if 3 out of the first 20 patients experience a grade 3 toxicity that has a probable or definite relationship to the study drug (islet cell product) or procedure. The Data and Safety Monitoring Board (DSMB) for the study will be given the stopping rules and this will be incorporated into their safety analysis plan.

8.5 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events. A DSMB charter has been created.

8.5.1 Independent Data and Safety Monitoring Board

The description and requirements of this Board are a Northwestern local convention (i.e. is not a description from federal regulations or ICH guidelines). The Data and Safety Monitoring Board (DSMB) is a group of professionals, experienced in clinical care and/or clinical research, assembled to provide additional safety oversight to this clinical study (and at least one biostatistician). This type of oversight differs from an Internal DSMB in that the Independent DSMB is independent of the investigator and sponsor, and is therefore generally also independent of the sponsor's and investigator's institution. Another important difference is that the DSMB can, and most typically does, conduct unblinded analyses. The DSMB should have a charter describing its function as well as an analysis plan for a pre-planned safety analysis(es).

There are three members that are listed on the charter and their roles are two are clinicians and one is a bio-scientist.

The DSMB will meet by phone conferencing and will review

- All adverse events of participants who receive study therapy, including islet transplant procedure and the product
- Recruitment/enrollment eligibility of participants
- Endpoint data
- Protocol deviations
- Subject withdrawals
- Blinded case report forms will be supplied to the DSMB
- The DSMB will meet every 6 months unless enrollment has not been successful and there is insufficient data for review or occurrence of serious adverse events suggesting the need for an earlier scheduled meeting
- The DSMB will record the summary of its various meetings and submit a written report to the PI

9 Data Handling and Record Keeping

We will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from participants and donors participating in this clinical trial. Medical and research records will be maintained in the strictest confidence. However, as a part of the quality assurance and legal responsibilities of an investigation, the investigational site must permit authorized representatives of regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress. Unless required by the laws permitting copying of records, only the coded identity associated with documents or other participant data may be copied (obscuring any personally identifying information). Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals. The investigational site will normally be notified in advance of auditing visits.

The Investigator will keep accurate records to ensure the conduct of the study is fully documented. The Investigator will ensure that all case report forms are legibly completed for every participant entered in the trial. The Investigator will also be responsible for regular inspection of the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness, consistency and accuracy of all documented data.

Electronic documents will be held by the Investigator in a password protected computer in a locked office and access to the office suite is by keycard alone. Paper documents are held in locked cabinets in an office suite which has keycard restricted access. The enrollment log and coded identifier lists will not be kept or maintained in the same format.

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product (i.e. human islets).

The records will be held on-site for 2 years after study closure and then off-site for an additional 13 years. Notification will be provided of the location of the off-site storage.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The formal consent of a subject, using the EC/IRB-approved consent form, will be obtained before any study procedures. This consent form will be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

Some tests and procedures are done only for this study and other tests and procedures are part of conventional medical care (not part of the research).

- The Comprehensive Transplant Center (CTC) will contact patient's health insurance providers to see if they will cover any portion of the costs associated with these transplant procedures (both standard of care as well as research-related procedures). This excludes Medicare and other government payment programs.
- The total cost of all the study procedures will be discussed with the patient prior to any study procedures.
- If the patient has insurance, the CTC will seek written confirmation from the health insurance company before starting any screening procedures for this study, regarding what portion of this study and its related costs will be covered. .
- If a patient's insurance does cover the cost of research related tests and procedures for this study, but requires the patient to pay co-pays or a portion of the bills to reach a deductible, the patient will be liable to cover those charges.
- If the patient's insurance does not cover the cost of research related tests and procedures for this study, there are discretional funds available from the Principal Investigator's account that will cover research procedures. Any remaining cost estimates will be discussed with the patient in detail. At that point, should the patient decide to continue with the study, s/he will be personally responsible for all costs related to research tests and procedures not covered by Northwestern University.
- The cost of all conventional medical care, including normal treatment of type 1 diabetes, will be billed to the patient or to the patient's health insurance company in the usual way. However, some health insurance plans will not pay the costs for people taking part in studies. The patient will check with their health plan or insurance company to find out what costs they will cover.
- The patient or their insurance company will be responsible for payment of long-term immunosuppression after participation in this study is complete. Patients will need to discuss their medical care beyond the completion of the study with their transplant doctor.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Northwestern University investigators will follow the University conflict of interest policy.

12.3 Subject Stipends or Payments

Subjects will be provided discounted parking coupon.

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the PI. Any investigator involved with this study is obligated to provide the PI with complete test results and all data derived from the study.

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Schedule of Events																					
Time points in Days	**Pre-SCR**	**SCR**	**WL/BL**	**0**	**3**	**7**	**14**	**21**	**28**	**42**	**56**	**90**	**120**	**150**	**180**	**210**	**240**	**270**	**300**	**330**	**365**
Visit number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Equivalent Wk/Mth						**W1**	**W2**	**W3**	**W4**	**W6**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**
Pre-Screening Questionnaire	X																				
Informed Consent	X	X*																			
Physical exam		X	B	X	X	X			X		X	X			X			X			X
Chest X-ray		X	B	X																	
Abdominal US		X				X															
ECG		X	B	X																	
Cardiac stress test (for cause)		X	2 Yrs																		
Quantiferon Gold		X																			
CBC (WBC w diff/plt)		X	Yearly	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry		X	Yearly	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipids		X	Yearly												X						X
Thyroid function (TSH)		X	Yearly																		
Pregnancy test (Females)		X	B	X																	
Serology		X	Yearly																		
EBV IgG		X																			
CMV IgG, CMV IgM		X	B	X																	
Coagulation (PT, PTT, INR)		X	B	X																	
Blood Type		X																			
HLA		X																			
Crossmatch			B	X																	
Fasting & post-prandial c-peptide					X	X															
PRA by flow cytometry		X	6mo/B									X			X			X			X
CMV by PCR			B									X			X						
First morning spot urine		X							X			X			X			X			X
HbA1c		X	Yearly/B									X			X			X			X
Fasting c-peptide									X		X	X	X	X	X	X	X	X	X	X	X
MMTT		X										X			X			X			X
PSA (Males)		X																			
Tacrolimus 12 hour trough level					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Schedule of Events												
Time points in Days	**390**	**420**	**450**	**480**	**510**	**540**	**570**	**600**	**630**	**660**	**690**	**720**
Visit number	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**
Equivalent Wk/Mth	**M13**	**M14**	**M15**	**M16**	**M17**	**M18**	**M19**	**M20**	**M21**	**M22**	**M23**	**M24**
Informed Consent												
Physical exam						X						X
Chest X-ray												
Abdominal US												
ECG												
Cardiac stress test (for cause)												
Quantiferon Gold												
CBC (WBC w diff/plt)	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X
Lipids						X						X
Thyroid function (TSH)												
Pregnancy test (Females)												
Serology												
EBV IgG												
CMV IgG, CMV IgM												
Coagulation (PT, PTT, INR)												
Blood Type												
HLA												
Crossmatch												
Fasting & post-prandial c-peptide												
PRA by flow cytometry						X						X
CMV by PCR												
First morning spot urine						X						X
HbA1c						X						X
Fasting c-peptide	X	X	X	X	X	X	X	X	X	X	X	X
MMTT						X						X
PSA (Males)												
Tacrolimus 12 hour trough level	X	X	X	X	X	X	X	X	X	X	X	X

Permission to Take Part in a Human Research Study
Do not sign this consent if today's date is later than the stated expiration date above.

Title of Research Study: A Phase 3 single center study of Islet Transplantation in Non-uremic Diabetic Patients

Investigator: Daniel Borja-Cacho, MD

Supported By: This research is supported by Northwestern University.

Your doctor, who is also responsible for this research study, interested in both your clinical care and the conduct of this research study. You have the right to discuss this study with another person who is not part of the research team before deciding whether to participate in the research.

Key Information:
The first few pages of this document include a summary of this study to help you decide whether or not to participate. Detailed information is provided after the summary.

Why am I being asked to take part in this research study?
We are asking you to take part in this research study because you have type 1 diabetes.

What should I know about a research study?
- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

Why is this research being done?
Type 1 diabetes is a problem in the pancreas. Islets are collections of a special type of cell in the pancreas that makes insulin. Insulin is a hormone that helps the body use glucose (sugar) for energy. In type 1 diabetes, the body's immune system destroys the islets in the pancreas so the body cannot produce enough insulin to control the amount of glucose in the blood. If this condition is not treated with insulin, it leads to various complications including hypoglycemia.

The usual treatment for type 1 diabetes is insulin, given by daily insulin shots or an insulin pump. However, this treatment does not always result in good control of blood glucose, and as a result, people with type 1 diabetes may develop damage to the heart, blood vessels, kidneys, and/or eyes. Whole pancreas transplant is an accepted treatment, for people who cannot control their blood glucose with insulin and/or people who also need a kidney transplant. Islet transplantation is another treatment for type 1 diabetes that is used as a standard therapy in some non-U.S. countries and is being studied as an investigational treatment in the United States. Investigational means that the treatment is not approved by the FDA and is not generally available outside of research studies. Islet cell transplantation is investigational in type 1 diabetes. Islet transplantation can be performed with less risk than whole pancreas transplant because it does not involve a major operation. However, whole pancreas transplantation, if successful, is more likely to control blood glucose without any need for insulin injections than islet transplantation.

We are inviting you to participate in this research because 1) you have type 1 diabetes that is poorly controlled, resulting in severe problems with low blood sugar and reduced awareness of low blood sugar (you may not know if your blood sugar is low), and you have never received an islet

cell transplant before; or 2) you have type 1 diabetes and have received at least one islet cell transplant in the past and have become insulin independent, but have now resumed partial or complete insulin requirement. The purpose of the study is to test the safety and effectiveness of an experimental procedure called islet transplantation, using standard medicines to prevent rejection of the islets.

Islets from an organ donor's pancreas will be removed and transplanted into your liver. Once these islets are transplanted into you, they begin to make and release insulin. If the transplanted islets begin to produce enough insulin you may be able to maintain better control of your glucose levels, reduce or eliminate your need for insulin injections for an unknown period of time, and reduce the complications of diabetes. It is likely that you will need a second and possibly a third transplant to eliminate your need for insulin. Whether you receive one, two, or three transplants, this study does not guarantee the transplanted islets will allow you to stop taking insulin.

How long will the research last and what will I need to do?

We expect that you will be in this research study for about two years from the time that you receive your last islet transplant. The length of your participation and the number of visits you will be required to attend will vary depending on how many transplants you receive. .

You will be asked to undergo screening procedures in order to make sure you are eligible to receive an islet transplant. If you are eligible you will be placed on an islet transplant waiting list. This means that if a suitable donor pancreas becomes available, you will be asked to come to the hospital as soon as possible, where you will undergo further testing to ensure that you are eligible to receive the islet transplant. If you are still eligible, you will receive the islet transplant.

While you are on the wait list you will be asked to record your blood sugar levels 4 times a day. You will also provide monthly blood samples in order to match you with potential donors.

After receiving the islet transplant, you will be asked to return to clinic for follow-up visits. At these visits, tests will be performed to monitor the islet transplant function. There will be up to 12 follow-up visits scheduled over 2 years. Additionally, you will be asked to have your blood drawn at a local clinic during those 2 years.

If the islet transplant is not producing enough insulin, you may be eligible to receive additional transplants.

More detailed information about the study procedures can be found under the section **What happens if I say "Yes, I want to be in this research"?**

Is there any way being in this study could be bad for me?

You will take immunosuppressive medications as a part of this study. Immunosuppressants (medicines to prevent your body from attacking the transplanted islets) can increase the chance that you will get a serious infection or cancer. Some of these infections can be life threatening. If you have any signs of infection (red skin, fever, chills, and/or green or white discharge from your nose or lungs) you should contact your study doctor right away.

Your body may attack or destroy your transplanted Islet cells. This is called rejection and you will need to start Insulin again if this occurs.

More detailed information about the risks of this study can be found under **"Is there any way being in this study could be bad for me? (Detailed Risks)"**

Will being in this study help me any way?

Permission to Take Part in a Human Research Study
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We cannot promise any benefits to you or others from your taking part in this research. However, the knowledge gained from these studies may help the researchers develop a safer and more effective treatment for type 1 diabetes that could help patients obtain better glucose control and reduce the risks of diabetes-related complications such as heart and kidney disease.

What happens if I do not want to be in this research?

Participation in research is completely voluntary. You decide whether or not to participate. If you choose to not participate, there will be no penalty to you or loss of benefit to which you are entitled.

Dr. Borja-Cacho will talk with you about the other options that are available. Other options include:

- continuing insulin treatment;
- getting a whole-pancreas transplant if you qualify; or
- participating in another islet or diabetes clinical trial.

Detailed Information:
The rest of this document includes detailed information about this study (in addition to the information listed above).

Whom can I talk to?

If you have questions, concerns, or complaints, or think the research has hurt you, talk to Dr. Daniel Borja-Cacho, the doctor in charge of this study. You can call him at # (312) 908-8147 Monday through Friday, from 9am-5pm and through the CTC answering service at (312) 695-8900 after hours and on weekends.

This research has been reviewed and approved by an Institutional Review Board (IRB). You may talk to them at (312) 503-9338 or irb@northwestern.edu if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

How many people will be studied?

We expect about 40 people will be in this research study.

What happens if I say "Yes, I want to be in this research"?

As a subject in this study, you will be asked to come to Northwestern Memorial Hospital, 251 East Huron Street, Feinberg 10 E, Clinical Research Unit, your involvement will last two years from the time that you receive your last islet transplant.

PRE-SCREENING
You will be asked to complete an eligibility questionnaire. This questionnaire will be used only to determine if you meet the minimum requirement for this study. If you do meet the minimum requirements you will be asked to provide your medical records to the research doctors.

If the research doctors think you will qualify to participate, some tests will be performed to make sure you are eligible. The research doctor will explain the tests that will be performed as part of your islet transplant evaluation. To take part in this study, you may also require additional tests that would not usually be part of an islet evaluation. One visit will be necessary to complete all of the screening tests, which will last approximately 1 day. The screening visits will include:

- A complete medical history and physical exam
- Several blood tests including ones to:
  - Test your organ function and your body's ability to make insulin and fight infections;
  - Look for antibodies (substances that would damage the transplanted islets);
  - Find out if you have been infected with certain viruses, such as hepatitis and HIV;
  - Test for the level of lipids (fats) and cholesterol in the blood
- Urine tests (a first morning spot urine)
- A blood test to determine if you currently have tuberculosis or have had it in the past;
- Pregnancy test (if you are female of child bearing potential);
- Ultrasounds which use sound waves to produce pictures of your internal organs;
- A chest x-ray;
- Tests to determine the health of your heart, including an electrocardiogram (ECG), and if indicated, a cardiac stress test or angiogram;
- Mixed Meal Test: Following an overnight fast (no food or liquids other than water), you will have a small blood sample drawn, then you will consume a drink containing known amounts of fat, protein and carbohydrate, similar to values in a typical meal. Your blood will be sampled at 60 and 90 minutes after you finish the drink;
- Provide blood sugar diaries of insulin usage and blood sugar readings before and after eating.

Additional reports will be required from other doctors, such as your diabetes doctor, eye doctor, and gynecologists (if you are female). The research doctors will tell you what types of reports will be needed.

After reviewing the results of the tests explained above, your research team will determine if you are eligible to participate in the studies. If you do not qualify, your research doctor will discuss the reasons with you and discuss other options available. If your research doctor determines you are eligible to participate, you will be placed on an islet transplant waiting list and will be asked to be available 24 hours a day, 7 days a week in case a suitable donor pancreas becomes available.

While you are on the waitlist Gift of Hope (GOH), our local Organ Procurement Organization (OPO) will send you a monthly mailer containing one blood collection tube for antibody screening. It is very important that you have these drawn at your local lab as soon as you receive the tube, and immediately send it back using the shipping materials provided. **These samples will be used to match you if an organ becomes available. Failure to send these blood samples each month may prevent you from receiving an organ transplant.**

HOSPITAL ADMISSION

When a compatible donor pancreas is found for you, you will be notified and asked to come to the hospital as soon as possible. Upon arriving at the hospital, you will be admitted as an inpatient for the transplant. When you are admitted, tests to measure organ function, your body's ability to fight infections, and urine collection will be repeated to make sure you are still eligible to participate. If you still meet the criteria to participate you will have the transplant on the first day of your inpatient hospital stay. You can expect to stay in the hospital for a total of 3 days.

You will receive several different medicines before, during, and after your transplant. These medicines will include immunosuppressants (medicines to prevent your body from attacking the transplanted islets), as well as medicines to help prevent blood clots and infections. Some medications may be taken for a couple of days or months after the transplant, and others will need to be taken for as long as the islet cells are functioning. Some of the medications can be substituted if you can't tolerate them and some may be taken at Dr Borja-Cacho's discretion.

THE TRANSPLANT PROCEDURE

The islets will be prepared for your transplant. There is a possibility that even though a compatible donor was found, the islets will not be suitable for transplant, because there may not be enough islets or the quality of the islets may be poor. If this happens, every effort is made to find you another compatible donor.

If there are no problems with the islets that are prepared for you, you will be brought into the hospital to begin the pre-transplant medications to prepare your body to receive the islet cell transplant. The research doctor will decide whether it is safer for you to have the transplant performed in radiology or in the operating room.

If your islet transplant team feels that doing the procedure in radiology is safer for you, you will be given medicines before the procedure to help you relax and you will get a shot of numbing medicine in your side. A physician will insert a long, thin, plastic tube just below your rib cage, and then guide it into your portal vein. Your portal vein is a large vessel through which blood flows to your liver. The research doctor will then deliver the islets from a plastic bag through the plastic tube into your liver over about 30 minutes. During the procedure your heart rate, blood pressure, and breathing rate will be monitored. At the end of the procedure, the plastic tube will be removed and the passage way that the tube took will be sealed to prevent bleeding. If the radiologist cannot get the plastic tube into the portal vein with this procedure, surgery may be required. If you need surgery, it will be done in the operating room.

If your islet transplant team feels that doing the procedure in the operating room is safer for you, you will be given general anesthesia to make you sleep. A small incision (about 2-3 inches) will be made in your abdominal wall. The surgeon will find a small vein next to your intestines and pass a small plastic tube into this vein toward the liver. After making sure the small plastic tube is in the right place the surgeon will infuse the islets into the portal vein. After the islets are injected, the thin plastic tube will be removed and the small vein will be tied off so it does not bleed. The incision will be closed with stitches, and a sterile dressing will be put over the incision. You will then go back to your hospital room.

To make sure the small plastic tube is in the right place, you will receive an injection of X-ray dye before the islets are infused, regardless of which procedure is done. The blood pressure in your portal vein will be checked often to make sure it does not get too high.

POST TRANSPLANT FOLLOW-UP

You will continue to take low doses of insulin as directed by the research doctor to avoid stressing the transplanted islets. If your transplanted islets are working well, your research doctor will continue to decrease the amount of insulin you need to take, or instruct you to stop taking your insulin for some period of time.

If the transplanted islets do not produce enough insulin to allow you to stop taking insulin shots, you may be eligible for an additional transplant after 3 months from the date of transplant. You may receive up to three transplants under this study. If the research doctor determines that you are not eligible for another transplant, you will be asked to come to the clinic on a reduced follow-up schedule and you will not receive additional islets under these studies. If the research doctor determines that you are eligible for another transplant, you will be placed back on the waiting list until another compatible donor pancreas becomes available for you. When a compatible donor pancreas is found for you, you will follow the same process that has already been described. If the time between transplants exceeds the two years follow up as outlined in this consent form, you will

be asked to continue to have monthly labs drawn until your subsequent transplant occurs. At the time of your subsequent transplant, you will return to the schedule of events listed below.

After the first, second, or third transplant procedure, you will return to the clinic for study follow-up visits as explained below:

You will return to the clinic at the following time points after your transplant:

- Days 3, 7 and 28
- Months 2, 3, 6, 9,12,15,18,21, and 24

You will be asked to visit your local laboratory for blood draws at the following time points:

- Days 14, 21 and 42
- Months 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, and 23

During the entire follow up period, we will communicate with you on a weekly basis (e.g. email communications) regarding other physicians and health care providers that you may have seen in the past week. If you have seen other physicians and health care providers in the past week, we will ask you to provide us with their contact information so that we can communicate with them directly regarding your transplantation and medications, particularly immunosuppressive drugs. If you have been prescribed with any new medications by these other physicians or health care providers, we will determine if these medications interfere with any of your transplant related medications. If drug to drug interactions are present between your newly prescribed medications and your transplant medications, they will be noted and appropriate actions will be taken to ensure adequate dosing and levels of the anti-rejection medications you are taking to protect your islets.

TESTS THAT WILL BE DONE AT FOLLOW-UP VISITS

You will have various tests completed during your follow-up visits. The research doctor will explain the tests to you and let you know what tests will be done at which visits. The following is a list of some of the different tests that will be done during the follow-up phase:

- Blood tests to monitor your general health, the condition of the transplanted islets, and your immune system;
- Urine tests, including first morning spot urine test;
- Ultrasounds which use sound waves to produce pictures of you internal organs;
- Tests to determine the health of your heart, including an electrocardiogram (ECG) to trace the electrical activity of your heart;
- Chest x-ray;
- Mixed Meal Tolerance Test;

	Day 3	Day 7	Wk 2	Wk 3	Wk 4	Wk 6	Mth 2	Mth 3
Physical exam	X	X			X		X	X
Ultrasound		X						
Blood tests	X	X	X	X	X	X	X	X
Urine tests					X			X
Mixed meal tolerance test								X
Review of subject diaries	X	X	X	X	X	X	X	X
Total Time Expected for Visit	180	240	30	30	60	30	60	180

Permission to Take Part in a Human Research Study
Do not sign this consent if today's date is later than the stated expiration date above.

(minutes)								

	Mth 4	Mth 5	Mth 6	Mth 7	Mth 8	Mth 9	Mth 10	Mth 11	Mth 12
Physical exam			X			X			X
Blood tests	X	X	X	X	X	X	X	X	X
Urine tests			X			X			X
Mixed meal tolerance test			X			X			X
Review of subject diaries	X	X	X	X	X	X	X	X	X
Total Time Expected for Visit (minutes)	30	30	180	30	30	180	30	30	180

	Mth 13	Mth 14	Mth 15	Mth 16	Mth 17	Mth 18	Mth 19	Mth 20	Mth 21	Mth 22	Mth 23	Mth 24
Physical exam						X						X
Blood tests	X	X	X	X	X	X	X	X	X	X	X	X
Urine tests						X						X
Mixed meal tolerance test						X						X
Review of subject diaries	X	X	X	X	X	X	X	X	X	X	X	X
Total Time Expected for Visit (minutes)	30	30	30	30	30	180	30	30	30	30	30	180

In addition to the tests listed above, you will be expected to continue completing a diabetes self-care diary and checking your blood sugar levels as directed by the research doctor. You will need to report your insulin usage, bring your glucometer to the center so the information stored in it can be downloaded, and turn in your self-care diary as directed by your research doctor.

HIV testing and reporting:
For this research study, you will be tested for HIV. HIV is the term used for the virus that produces HIV infection and may ultimately lead to AIDS. Your blood will be drawn to test for HIV. The study doctor must follow the Illinois AIDS Confidentiality Act (An Illinois law that sets up how HIV testing must be done and protects the confidentiality of information about someone's HIV status.

You must be told that you are being tested for HIV and give consent. By signing this consent form and agreeing to be in this research, you are agreeing to the HIV testing.

The test involves taking 1/5 teaspoon of your blood.

You have a right to know the results of the test. If you test positive you will be given more tests to confirm the results of the first test. If you are HIV positive, the study doctor will also give you a list of referrals for further information and counseling.

What are my responsibilities if I take part in this research?

If you take part in this research, you will be responsible to;

1. Attend study visits so that the researchers can ensure your safety.
2. Inform the research team of any hospitalization or adverse events.
3. Inform the research team when you go out of town in case an organ becomes available.

What happens if I say "Yes", but I change my mind later?

You can leave the research at any time; it will not be held against you.

If you decide to leave the research, contact the research team so that the research doctor can take the necessary steps to remove you from the study. For example your medication may need to be altered or tapered gradually. Some follow-up tests may be needed to avoid unwanted adverse effects.

Choosing not to be in this study or to stop being in this study will not result in any penalty to you or loss of benefit to which you are entitled. Specifically, your choice not to be in this study will not negatively affect your right to any present or future medical treatment.

If you decide to withdraw from the study we may ask you to come into the clinic for a final evaluation. You are not required to keep this appointment, but it would be very beneficial to the research study and your health. In addition, you should consult Dr. Borja-Cacho who will discuss future treatment and procedures for your continued care when you are no longer in this study.

If you stop being in the research, already collected data may not be removed from the study database. You will be asked whether the investigator can collect data from your routine medical care. If you agree, this data will be handled the same as research data.

Detailed Risks: Is there any way being in this study could be bad for me?

Taking part in this study may involve the following risks, as with any medication or surgical procedure, there is a risk that a rare or previously unknown side effect, drug interaction, or allergy can occur. You may have more problems as a result of participating in this islet transplant research than you would have if you continued insulin treatment alone. These unknown risks may affect you during your participation in the research and/or at some point in the future.

RISKS FROM THE ISLET TRANSPLANT PROCEDURE:
The following risks are associated with the procedure to transplant the islets:

- moderate pain or discomfort;
- bleeding from a puncture to your liver, which may require a blood transfusion;
- damage to your liver or blood vessels in your abdomen, which may require surgery;
- damage to your gallbladder, which may lead to the removal of your gallbladder;
- bleeding as a result of the blood thinners used to prepare the islets;
- blood clot in the vein going to your liver after the procedure and causing damage, which may get better on its own or may lead to the need for a liver transplant;
- slowed or stopped breathing as a result of the sedation used for the procedure;
- fluid around the lungs;
- death from complications (this risk is rare but possible); and
- liver or kidney injury that may or may not resolve.

RISK OF REJECTION:
Your body may attack and destroy your transplanted islets. This is called rejection. If you reject your islets, you will need to start using insulin again to keep your glucose under control. If you need to take insulin again, you will need approximately the same amount of insulin you were taking before the transplant. If the islets are working partially, you will require less insulin. We have no evidence that you could require more insulin than you were taking before transplant.

RISK OF DEVELOPING ANTIBODIES

Permission to Take Part in a Human Research Study
Do not sign this consent if today's date is later than the stated expiration date above.

Your body has the ability to recognize foreign cells. After you receive your transplant, you may develop antibodies against your donor. Antibodies are proteins made by the body to protect itself from foreign substances. These antibodies can develop in anyone who receives a transplant, but they are more likely to develop if you stop taking your immunosuppression. If you develop antibodies against the transplanted islets, the following risks may affect you:

1. You may reject your islets.
2. If you require a transplant in the future, either another islet transplant or an organ such as a kidney, your time waiting on a transplant waiting list will probably be longer than if you had not developed antibodies because it will take longer to find a compatible donor.
3. If you require a transplant in the future, your transplanted organ may not work as well or last as long as it would have if you had not developed antibodies.

RISK OF INFECTIONS:
In addition to infection that may result from the transplant procedure, the preparation containing the islets could be contaminated and cause an infection. You will receive antibiotics during the transplant to reduce the risk of infection. Immunosuppression and being in the hospital will also increase your risk of infection. You, like all other people who get transplants, will receive medications to prevent infections.

RISKS FROM BLOOD DRAW:
The risks of having blood drawn include temporary discomfort or pain, bruising at the site of puncture, fainting, and infection or a small blood clot or swelling to the vein and area surrounding where the blood is drawn. Also, when a large amount of blood is taken, you may get iron deficiency and/or anemia (low red blood cell count). These conditions may cause you to feel tired or weak. If that happens, other medications may be required to help reduce these side effects.

It is important for you to know that the amount of blood that will be drawn for research purposes during the study will never exceed 100 ml (7 tablespoons) during any single visit.

RISKS FROM THE METABOLIC STIMULATED TESTS:
During this study you will have tests done to measure your glucose level in response to a variety of substances that you eat. During these tests your blood glucose may go up, which may require you to get a shot of insulin.

There may be slight discomfort in your arm or hand during the inserting of the catheter into the vein. Occasionally, a small blood clot may form where the catheter is inserted. This may result in a small lump that will disappear. Occasionally, a small amount of bleeding may occur around where catheter is placed. On rare occasions, a local infection may occur around the catheter. There is a very slight possibility of a change in heart rate, blood pressure, or temperature. These will be checked frequently during these tests.

RISKS FROM RADIATION:
If you take part in this voluntary research, you may have one or more medical imaging studies which use radiation. The tests, procedures, or treatments you may have over the course of the research may include up to three (3) sets of imaging and location of the hepatic portal vein for islet infusion, and two (2) Chest – x-rays, to rule out active infections (TB).

To give you an idea about how much radiation exposure you may receive, we will make a comparison with an every-day situation. Everyone receives a small amount of unavoidable radiation each year. In the Chicago area, one receives about 300 mrem1 on an annual basis from this background radiation and man-made sources. Some of this radiation comes from space and

some from naturally-occurring radioactive forms of water and minerals. This research may give your body the equivalent of approximately 3.1 years' worth of this natural radiation.

A possible health problem seen with radiation exposure is the development of cancer later in life. The effects from radiation exposures are accumulative and some studies suggest that there is always a risk of cancer, even from small doses of exposure; however, very unlikely. This extra cancer risk is higher at younger ages and for girls and women.

It is possible that having several of these tests may add to your risk of injury or disease. When deciding to enter this study one should consider past and future contact with radiation. Examples of contact with radiation include x-rays taken for any reason or radiation therapy for cancer treatment. The radiation dose we have discussed is what you will receive from this study only and does not include any exposure you may have received or will receive from other radiological tests. You must inform your physician if you are pregnant or believe that there is likelihood of pregnancy; no matter how remote, before and during this research study.

RISKS FROM IMMUNOSUPPRESSION:
Immunosuppressants (medicines to prevent your body from attacking the transplanted islets) can increase the chance that you will get a serious infection or cancer. Some of these infections can be life threatening. If you have any signs of infection (red skin, fever, chills, and/or green or white discharge from your nose or lungs) you should contact your study doctor right away.

RISKS FROM SPECIFIC IMMUNOSUPPRESSION MEDICATIONS:

Alemtuzumab (Campath 1H®):
Duration of therapy is on the day 0 of first transplant and day 0 of second or third transplants, if deemed appropriate by the study PI based on your blood counts.

Infusion related side effects include: fever, nausea, vomiting, hypotension (low blood pressure), rigors, fatigue, shortness of breath, bronchospasm (sudden, uncontrolled narrowing of airways in lungs), rash, and chills. To decrease or stop these symptoms, you will be premedicated (given medication before the alemtuzumab) 30-60 minutes before you study drug is given.

Basiliximab (Simulect):
Possibly used instead of alemtuzumab if a 2nd or 3rd transplant if deemed appropriate by the study PI based on your blood counts.

Duration of therapy is on the day of transplant and on day 4 post-transplant.

Common side effects include: constipation, nausea, diarrhea, vomiting, abdominal pain, heartburn, indigestion, bloating, swelling of the hand and/or feet, trembling, headache, dizziness, infection, infrequent urination, painful urination, kidney damage, chest pain, fever, pain, fatigue, high blood pressure, low blood pressure, shortness of breath, coughing, fluid in the lungs, poor wound healing, acne, insomnia, fast heart rate, blood clots, bleeding, fluid collections, high blood sugar, and in rare circumstances a severe allergic reaction.

***Tacrolimus (Prograf):**
Duration of therapy is from 1 day after transplant through the duration of the graft function.

Common side effects of (Prograf) include: high blood pressure, high blood sugar, diabetes, and kidney damage.

Other side effects of (Prograf) include: trembling, headaches, burning in the hands and/or feet, itchy skin, increased levels of potassium in the blood (which can cause nausea and an irregular heartbeat), increase in cholesterol and or triglyceride levels in the blood, unsteady movements or clumsiness, thickening of the heart muscle, insomnia, abdominal pain, diarrhea, nausea, and infection. Less common but more serious side effects include inflammation of the lung tissue, BK nephropathy (in subjects who receive a renal transplant), a type of kidney infection; posterior reversible encephalopathy syndrome (PRES), a combination of side effects including, headaches, confusion, seizure, and vision problems: and progressive multifocal leukoencephalopathy (PML), a serious infection that can lead to disability or death.

***Sirolimus (Rapamycin, Rapamune ®)**
Duration of therapy is from the day of transplant through the duration of graft function, including after a second or third islet transplant.

Common side effects of Rapamune® include: high blood pressure, elevated cholesterol and triglyceride levels, ulcers (sores) in your mouth that are similar but often larger than cold sores, infection involving the urinary tract, decreased number of platelets which help clot the blood, and problems with wound healing.

Other side effects of Rapamune® may include: infection, ovarian cysts, diarrhea, abdominal pain, headache, swelling in the arms or legs, nausea, fever, anemia (low blood iron levels), joint pain, kidney damage, swelling of the lung tissue, swelling of the large intestine, milk level of kidney dysfunction caused by swelling and cancer.

***Mycophenolate Mofetil (CellCept®) or Mycophenolate Sodium (Myfortic®):**
Duration of therapy is from day of transplant through the duration of graft function.

Common side effects of CellCept include: abdominal pain, diarrhea, upset stomach, vomiting, leukopenia (a decrease in white blood cells), and a higher risk of certain serious infections, including BK nephropathy, a type of kidney infection, and progressive multifocal leukoencephalopathy (PML), a serious infection that can lead to disability or death. CellCept is also associated with birth defects and pregnancy risks, including loss of the fetus and pure red cell aplasia, a type of anemia where the bone marrow stops making red blood cells.

***It will be up to the principle investigator's discretion to choose the combination of immunosuppression therapy that best suits each subject.**

Etanercept (Enbrel):
Duration of therapy is on the day of transplant and on days 3, 7, and 10 post-transplant.

An injection site reaction such as redness, pain or swelling is a common side effect of Enbrel .

Other side effects of Enbrel may include: headache, nausea, muscle tremors, cancer, immune-system damage to multiple organs, failure to produce red blood cells (which can be fatal), blurred vision, loss of bladder and/or bowel control and partial or complete paralysis (these neurological problems usually go away partially or completely after you stop taking the drug), in very rare cases serious infection and death have occurred.

Enoxaparin (Lovenox®):
Duration of therapy is on day 2 of transplant through day 7 after transplant.

The side effects may include: bleeding, anemia, fever, and low platelets.

Pentoxifylline (Trental®):
Duration of therapy is on the day of transplant through day 7 after transplant.

The side effects may include: heartburn, nausea, vomiting, dizziness, headache.

Valacyclovir (Valtrex®):
To prevent against possible cytomegalovirus (CMV) infection (CMV is one of the herpes viruses), patients who are CMV negative who receive islets from CMV negative donors will receive 500 mg of Valacyclovir orally, every day, from the day of the transplant through 6 months post-transplant. This is standard of care treatment post-transplant.

The side effects may include: confusion, agitation, depression, weakness, headache, nausea, vomiting, diarrhea, stomach pain, dizziness, rash, hives, changes in urination and problems with coordination.

Valganciclovir (Valcyte®):
To treat CMV infection, patients who are CMV positive, patients whose donors are CMV positive, or patients where both the and donor are CMV positive, will receive 450 mg of Valganciclovir, orally, every day, from the day of transplant through 3 months post-transplant. This is standard of care treatment post-transplant.

The side effects may include: decreased production of white and red blood cells by your bone marrow, fever, blood clots, and decreased appetite.

Trimethoprim/Sulfamethoxazole (Septra SS®/Bactrim®):
Duration of therapy is on the day after transplant through the duration of follow-up.

The side effects may include: low white blood cell and platelet counts, anemia, fever, chills, vertigo, seizures, meningitis, depression, reduced appetite, nausea, vomiting, liver damage, large bowel inflammation, rash, hives.

Atovaquone (Mepron®) may be substituted for Bactrim
Duration of therapy is on the day after transplant through the duration of follow-up.

The side effects may include: upset stomach, diarrhea, constipation, headache, sleeping difficulties, sweating, dizziness, drowsiness, altered sense of taste.

Clotrimazole (Mycelex Troche®):
Duration of therapy is on the day of transplant through month 3 post transplant.

The side effects may include: nausea, vomiting, stomach distress, and diarrhea.

Nystatin oral suspension: may be substituted for Mycelex Troche
Duration of therapy is on the day of transplant through month 3 post transplant.

The side effects may include: nausea, vomiting, diarrhea, and stomach distress

Rituximab (Rituxin):
Duration of therapy is on the day of transplant.

The side effects may include: infusion reactions, fever, chills, infection, nausea, diarrhea, headache, muscle spasms, swelling, low blood cell counts, and weakness.

Simulect (Basiliximab)

Duration of therapy is only on the day of transplant.

Diarrhea, constipation, nausea, peripheral edema, tremor, Anemia, hypertension, vomiting, Hypomagnesemia, insomnia, headache and fatigue.

RISK OF PSYCHOLOGICAL STRESS:
Participation in this research will involve a transplant procedure and the need to take several different medications. The requirements of these research studies may cause psychological stress.

There is the risk that you may find out that you are HIV positive. These results may be emotionally upsetting and may also cause you psychological distress.

Be sure to tell your doctor immediately if you experience any psychological symptoms, for example anxiety or depression.

What do I need to know about reproductive health/sexual activity if I am in this study?

The effect of the study drugs on human sperm and eggs has not been studied. The effects on the developing fetus of using the study drug during pregnancy and the risk of birth defects are also unknown or may be unforeseeable. However, animal studies have shown that this drug can cause fetal death and developmental delay of the fetus and newborn. Therefore, both men and women should not attempt pregnancy and women should not be pregnant or breast-feeding while participating in this study. If sexually active, both men and women must use an effective method of birth control throughout the duration of the study. If you start taking CellCept® or Myfortic® you will have to use two acceptable forms of birth control. Barrier contraceptives (condoms or diaphragm) with spermicide, intrauterine devices, hormonal contraceptives, oral contraceptive pills, surgical sterilization, and complete abstinence are examples of effective birth control methods. Only methods that use condoms provide adequate protection against sexually transmitted diseases.

If you or your partner become pregnant while taking the study drug or the other anti-rejections medications, it is important that you notify your study nurse/physician immediately. You may be required to stop or change medications at which time other treatment options will be discussed with you. Certain drugs may also interact with birth control pills and reduce their effectiveness.

If you are considered to be postmenopausal, you are not required to use contraception while in this study. Rarely, women considered to be postmenopausal become pregnant. If you suspect that you become pregnant while taking the study drug, it is important that you tell the study nurse/doctor immediately. You may have to stop the study drug. Other treatment options will be discussed with you if you stop the study drug.

Will it cost me anything to participate in this research study?

There will be tests and procedures that are done only for this study and other tests and procedures that are part of your conventional medical care (not part of the research).

- If you have insurance and choose to sign this consent form and participate in this study, with your permission:
    - We will contact your insurance provider to see if they will cover any portion of the costs associated with these transplant procedures (both standard of care as well as

research-related procedures). This excludes Medicare and other government payment programs.
    - We will seek written confirmation from your insurance company regarding what portion of this study and its related costs your insurance provider will be covered.
    - The total cost of all the study procedures will be discussed with you prior to any study procedures.
    - If your insurance does cover the cost of research related tests and procedures for this study, but requires you to pay co-pays or a portion of the bills to reach a deductible, you will be liable to cover those charges.
    - If your insurance does not cover the cost of research related tests and procedures for this study, there are discretional funds available from the Principal Investigator's account that will cover research procedures. Any remaining cost estimates will be discussed with you in detail. At that point, should you decide to continue with the study, as you will be personally responsible for all costs related to research tests and procedures not covered by Northwestern University.

- If you do not have insurance and choose to sign this consent form and participate in this study:
    - There are discretional funds available from the Principal Investigator's account that will cover research procedures. Any remaining cost estimates will be discussed with you in detail. At that point, should you decide to continue with the study, as you will be personally responsible for all costs related to research tests and procedures not covered by Northwestern University.

All post-transplant safety and follow up will be completed in full, irrespective of the funding source.

The cost of your conventional medical care, including all normal treatment of type 1 diabetes, will be billed to you or to your health insurance company in the usual way. However, some health insurance plans will not pay the costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for before you agree to participate.

You or your insurance company will be responsible for payment of long-term immunosuppression.

Will being in this study help me in any way?

If you agree to take part in this research there may be no direct medical benefit to you. The knowledge gained from these studies may help the researchers develop a safer and more effective treatment for type 1 diabetes that could help patients obtain better glucose control and reduce the risks of diabetes-related complications such as heart and kidney disease. However, we do not guarantee or promise that you will receive any of these benefits.

What happens to the information collected for the research?

Efforts will be made to limit the use and disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete secrecy. Organizations that may inspect and copy your information include the institutional review board (IRB) , other representatives of this institution, and the US Department of Health and Human Services.

The sponsor, monitors, auditors, the IRB, the Northwestern University Office for Research Integrity, the US Office of Research Integrity (ORI), the US Office for the Protection of Human Research Protections (OHRP), and the US Food and Drug Administration (FDA) may be granted direct access to your medical records to conduct and oversee the research. By signing this document, you are authorizing this access. We may publish the results of this research. However, we will keep your name and other identifying information confidential.

Permission to Take Part in a Human Research Study
Do not sign this consent if today's date is later than the stated expiration date above.

A description of this clinical trial will be available at http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Data Sharing
De-identified data from this study may be shared with the research community at large to advance science and health. We will remove or code any personal information that could identify you before files are shared with other researchers to ensure that, by current scientific standards and known methods, no one will be able to identify you from the information we share. Despite these measures, we cannot guarantee anonymity of your personal data.

Can I be removed from the research without my OK?
You may be removed from the study without your consent at any time. Reasons why you may be removed from the study include, but are not limited to the following:

- Dr. Borja-Cacho determines that it is not in your best interest to continue in the study;
- An adverse event, injury or medical condition which may place you at risk of further complications if you continue to participate
- You are unable to complete required study treatments and examinations; or
- The study is stopped by the Institution or by the Food and Drug Administration (FDA) or other health authorities.

If you are removed from the study Dr. Borja-Cacho will contact you to discuss the procedures and appropriate future treatment for you continued care.

What else do I need to know?
If you become ill or are injured as a result of this study (medications, devices or procedures), you should seek medical treatment through your doctor or treatment center of choice. You should promptly tell the study doctor about any illness or injury.

The hospital [university, researchers] will not pay for medical care required because of a bad outcome resulting from your participation in this research study. This does not keep you from seeking to be paid back for care required because of a bad outcome.

You will not be paid for your participation in this study.

You will get a parking voucher for taking part in this research study. It will be given to you at the end of each study-related visit.

HIPAA Authorization
We are committed to respect your privacy and to keep your personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal health information that includes health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number or social security number. Your health information we may collect and use for this research includes:

- All information in a medical record

You have the right to inspect and copy the mental health and developmental disabilities records that will be collected as part of this study.

Permission to Take Part in a Human Research Study
Do not sign this consent if today's date is later than the stated expiration date above.

This consent expires on 12/31/2050. After this date, Northwestern University may not gather new information about you, use or disclose your personal health information collected in this study for any purpose other than the research study described in this consent unless Northwestern University obtains permission to do so from you. Illinois State Law permits use and disclosure of your mental health information only to the extent specified in this document.

During this study you may be coming to a Northwestern Memorial Healthcare Corporation entity (for example, Northwestern Memorial Hospital, Prentice Women's Hospital) for research appointments or to get clinical services, such as lab tests, needed for the study. When that happens, you will be scheduled for these services through the NMHC computer system. When a clinical exam or lab is done by NMHC or one of its employees for the purpose of this research study, that information will be kept in both NMHC's clinical records and in the study records.

The following clinical providers may give the researchers information about you: all current and previous health care providers, including but not limited to the Shirley Ryan AbilityLab (SRALAB), Northwestern Medical Group (NMG), Northwestern Memorial Hospital (NMH), Northwestern Lake Forest Hospital (NLFH).

Once we have the health information listed above, we may share some of this information with the following offices or entities outside of Northwestern University and its clinical partners (or affiliates): the Northwestern University Institutional Review Board Office and Office for Research Integrity; the US Office of Research Integrity; the US Office for Human Research Protections; the US Food and Drug Administration.

Any research information shared with outside entities will not contain your name, address, telephone or social security number or any other personal identifier unless disclosure of the identifier is necessary for review by such parties or is required by law or University policy [except that such information may be viewed by the Study sponsor and its partners or contractors at the Principal Investigator's office].

The following entities may receive your health information:

- Authorized members of the Northwestern University workforce, who may need to see your information, such as administrative staff members from the Office for Research, Office for Research Integrity and members of the Institutional Review Board.
- Clinical affiliates, including but not limited the Shirley Ryan AbilityLab (SRALAB), Northwestern Medical Group (NMG), Northwestern Memorial Hospital (NMH), Northwestern Lake Forest Hospital (NLFH), and the Ann & Robert H. Lurie Children's Hospital of Chicago (Lurie Children's).
- Clinical affiliates, including but not limited to Northwestern Medical Group (NMG), Northwestern Memorial Hospital (NMH), and Northwestern Lake Forest Hospital (NLFH), for purposes including, but not limited to, the affiliate's provision of care to you and/or the affiliate's scheduling of appointments and/or billing activities.
- Other University research centers and University contractors who are also working on the study,
- Study monitors and auditors who make sure that the study is being done properly,
- Government agencies and public health authorities, such as the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS).
- Registries or other research-related databases.
- The study doctor must report positive HIV tests to the Illinois Department of Public Health (IDPH). The IDPH keeps track of all persons in the state with positive HIV tests. The database that keeps track of this information is coded so that your name does not appear

with your HIV status. You are given a unique identification number. This helps keep your name private.

Those persons who get your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission. However, Illinois law does not allow the re-release of HIV/AIDS, genetic testing, mental health and developmental disabilities information by the receivers of the information except in precise situations allowed by law.

Also, Federal law/42 CFR Part 2 prohibits unauthorized disclosure of these records.

The results of this study may also be used for teaching, publications, or for presentation at scientific meetings.

Unless you revoke your consent, it will expire 12/31/2050.

Although you may revoke consent to participation in this research at any time and in any format, you must revoke authorization for use or disclosure of your health information in writing. To revoke your authorization, write to:

Daniel Borja-Cacho, MD
Northwestern University
Comprehensive Transplant Center
676 N. St. Clair Street, Suite 1900
Chicago, IL 60611

You do not have to authorize the use or disclosure of your health information; however, you will not be allowed to take part in this research study. If you do not authorize the use or disclosure of your health information, it will not affect your treatment by health care providers, or the payment or enrollment in any health plans, or affect your eligibility for benefits.

A copy of this signed consent document, information about this study, and the results of any test or procedure done may be included in your medical records and may be seen by your insurance company.

Permission to Take Part in a Human Research Study
Do not sign this consent if today's date is later than the stated expiration date above.

Signature Block for Consent:

Your signature documents your permission to take part in this research. You will be provided a copy of this signed document.

_____ _____
Signature of Participant Date

_____
Printed Name of Participant

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Person Obtaining Consent

Witness for Mental Health Information

My signature below documents that the information in the consent document and assent process and any other written and verbal information was accurately explained to, and apparently understood by, the participant, and that consent was freely given by the participant.

_____ _____
Signature of Witness to Consent/Assent Process Date

_____
Printed Name of Person Witnessing Consent/Assent Process