Coordinating Center for:
International Solid Organ Transplantation Tolerance (ISOrTT) Registry

1. Objective and Specific Aims

The ISOTTO Registry is a multi-center, international observational study designed to prospectively follow the outcomes of subjects who have been successfully withdrawn from immunosuppression for a period of at least twelve months following solid organ transplantation. This web based registry will be used by participating international centers to: 1. prospectively record the natural history and outcome of drug withdrawal after pediatric and adult solid organ transplant across all organ systems; and 2. provide participants with current information regarding organ transplant tolerance and available research studies.

It is anticipated that sustained, long term operational tolerance will be documented in kidney, liver and small bowel transplant recipients. We hypothesize that positive predictive clinical factors for successful drug withdrawal will include lack of auto-immune disease history, lack of antecedent multiple rejection history, degree of HLA matching, living donor transplant, and age at transplant.

Specific Aim 1: A. To establish an international network of transplant centers for the recruitment and follow-up of solid organ transplant recipients who have been successfully withdrawn from immunosuppression using a web based registry. B. To establish a patient and public access portion of the web site to provide current information on transplantation tolerance and access to ongoing studies of transplant tolerance, as in Aim 3.

Specific Aim 2: To describe the natural history of withdrawal of immunosuppression in outcomes measures of survival, time off immunosuppression, graft function, growth, acute and/or chronic rejection, graft loss and immunosuppression history.

***Specific Aim 3*:** To offer access to current and future studies of tolerance mechanisms at participating centers and to facilitate hypothesis generation for future studies involving transplantation tolerance.

2. Background and Significance

Sporadic clinical transplant tolerance has been achieved following solid organ transplantation, most commonly after liver transplantation. Operational tolerance, defined as long term (>12 month) freedom from all immunosuppression in patients with normal graft function was first seen in both non-compliant patients and patients withdrawn for emergent infectious or malignant indications. Individual centers have also reported the ability to slowly wean patients from immunosuppression over time or emergently for specific indications after liver and kidney transplant. No multi-center registry or prospective analysis of patients withdrawn from immunosuppression currently exists.

For reasons that are unclear, patients transplanted as children have been more likely to achieve this operational tolerance than those transplanted as adults . Estimates of ability to wean immunosuppression successfully following liver transplant vary from 3-5% of cases. In very carefully selected patient populations, up to 20% of patients may be potentially weaned. In live

donor transplant populations, up to 15% of all patients may be successfully withdrawn from immunosuppressive medications . Long term follow-up of patients successfully withdrawn, however, is limited to individual center reports. The true incidence and ability to withdraw drugs after liver or other organ transplants is unknown as is the natural history of these patients after drug withdrawal.

A registry of these patients would allow better characterization of the natural history of drug withdrawal and help develop predictive clinical factors that favor drug withdrawal. Furthermore, this database will facilitate entry of these patients into ongoing or developing trials of assay development. The development of predictive, reproducible assays that can identify patients who may safely be withdrawn from immunosuppression or conversely identify those who require maintenance immunosuppression will be critical to minimizing long term morbidity and mortality in organ transplantation Assays performed in this unique patient population, such as cytokine gene polymorphisms and dendritic cell subsets, have yielded encouraging but preliminary results . Other centers have reported the importance of T regulatory cells as a potential mechanism in their tolerant patients and are identifying gene profiles associated with tolerance .

The two largest single center experiences in drug withdrawal after solid organ transplantation are from Pittsburgh and Kyoto . Both institutions, as well as select institutions from Europe and North America, will collaborate to build on this preliminary data. The Pittsburgh experience has primarily focused on deceased donor transplantation. We currently follow 47 patients who have been withdrawn from immunosuppression after liver transplant by planned physician intervention (protocol), emergently due to infectious disease indications (mostly EBV or PTLD indications), as well as those who self-weaned medication but are still under medical supervision with laboratory assessments. As noted in Table 1 , most of these patients were children at the time of transplantation. Return to immunosuppression has been rare (1/48), no graft loss has occurred, and no chronic rejection has been documented. Mean time off immunosuppression is over 10 years in the prospectively weaned cohort.

TABLE 1 Operationally tolerant liver transplant recipients University of Pittsburgh- long term follow-up (1992-2006)

Method of drug withdrawal	**Protocol**	**Emergent**	**Non-Adherance**
# Patients	28	13	6
Median Age at Tx (years)	3.8	1.6	11.4
Years from Tx to Wean	5.7	3.13	7.3
Years from Wean to drug cessation	2.2	N/A	N/A
Mean Years off drugs currently	10.8	11.7	17.1

The Kyoto group has documented 87 of 659 children (15%) who underwent live donor liver transplant between 1990 and May 2005 and have achieved complete withdrawal of immunosuppression. Taken in aggregate, predictive factors for successful drug withdrawal have included pediatric age at transplant, lack of autoimmune disease, and live donor transplant. A smaller cohort of 18 patients who underwent drug withdrawal at King's College London England also demonstrated the positive predictive effect of non-auto-immune disease, as well as fewer donor-recipient HLA mismatches and low incidence of pre-weaning rejection history.

3. Research Design and Methods

This is a multi-center prospective descriptive study utilizing a secure, web based registry designed to follow tolerant abdominal solid organ transplant recipients. Transplant recipients of abdominal solid organs (liver, kidney, intestine) who have been off immunosuppression for at least 12 months will be recruited for the study. Up to 30 centers in the United States, Asia and Europe will participate in this registry. Up to 10,000 participants across all organs will be enrolled in this registry. As this is a registry which utilizes clinical data points, all that is required by the participant is informed consent to enter the data into the web based registry, which is managed by the University of Pittsburgh. Once a person consents, the investigator(s) who will also be a member of the clinical care team will enter the enrollment data into the web based registry. The information contained in the web based registry will not contain the participant's name, address, social security number or hospital ID number. When a new participant is entered in the system, the system will assign a unique code to that individual, and each site/investigator will be responsible for keeping the linking information in a secure location. Once a year, the investigator(s) at each site will collect and enter the update information for each participant enrolled in the registry. The coordinating center manager or designee will monitor the update information and send out reminders to the individual sites as needed. The data in the registry will be kept indefinitely. The data within the registry will be under the control of the PI, Dr. George Mazariegos.

Collaborators at other sites will have access to the de-identified information contained in the registry for the purpose of manuscript preparation, hypothesis generation, preliminary data, or other needs as approved by the Principal Investigator.

Collaborating Centers: The following is a list of collaborating centers, investigator(s) and organ type.

North America

University of California, San Francisco (San Francisco, CA); Sandy Feng; LIVER

Stanford University Medical Center (Stanford, CA); Ricardo Castilo, Carlos Esquivel, William Bergquist, Kenneth Cox, Minnie Sarwal; LIVER, KIDNEY

University of Miami (Miami, Florida); Tom Kato; LIVER, INTESTINE

Children's Memorial Hospital (Chicago, IL); Estella Alonso; LIVER

Children's Hospital (Boston, MA); Heung Bae Kim; LIVER, INTESTINE

University of Michigan Ann Arbor (Ann Arbor, MI); John Magee; LIVER

Washington University (St. Louis, MO); Ross Shephard, Michelle Nadler; LIVER

University of Nebraska Medical Center (Omaha, NE); Deb Sudan; LIVER, INTESTINE

Mount Sinai (New York City, NY); Kishore Iyer; LIVER, INTESTINE

University of Pittsburgh Medical Center (Pittsburgh, PA); Ron Shapiro, George Mazariegos, Steve Webber, Kareem Abu-Elmagd, Rakesh Sindhi; LIVER, KIDNEY, INTESTINE

University of Washington Medical Center (Seattle, WA); Simon Horslen, Jorge Reyes; LIVER, INTESTINE

Asia
Kyoto University (Kyoto, Japan); Takaaki Koshiba; LIVER

Europe
St. Luc's (Brussels, Belgium); Raymond Reding, Jean Bernard Otte; LIVER

Birmingham Children's Hospital (Birmingham, England); Carla Lloyd; LIVER

King's College (London, England); Anil Dahwan; LIVER

INSERM (Nantes Cedex, France); Jean Paul Soulillou; LIVER, KIDNEY

University Medical Center Hamburg-Eppendorf (Hamburg, Germany); Martin Burdelski; LIVER

Ospedali Diuniti Di Bergamo (Bergamo, Italy); Michelle Colledan; LIVER

ISMETT (Palermo, Italy); Marco Spada; LIVER

Bambino Jesu (Rome, Italy); Jean de Ville de Goyet; LIVER, INTESTINE

Hospital Clinic of Barcelona (Barcelona, Spain); Alberto Sanchez Fueyo; LIVER

Data Collection and Statistical Support: This is a multi-center descriptive study designed to have a centralized registry of tolerant organ transplant recipients as well as to follow the natural history of these recipients. As such, there are no calculations used to estimate sample size.

4. Human Subjects
Abdominal solid organ transplant recipients 1 year of age and older who have been off immunosuppression for at least 12 months and are followed clinically at one of the participating centers will be included in this study. The racial, gender and ethnic characteristics of the proposed subject population reflects the demographics of the surrounding areas and/or the patient populations of the collaborating centers. We shall attempt to recruit subjects in respective proportion to these demographics. No exclusion criteria shall be based on race, ethnicity, gender or HIV status. Up to 10,000 subjects will be included in this registry across all collaborating centers and organ systems.

Inclusion of Children in Research: Children one year of age or older will be included in this study. Many of the collaborating centers have subspecialties in pediatric transplantation; in addition, many of the investigators at the centers have experience in pediatric transplantation. As

this is a data only research registry, the study meets the regulatory criteria for **Criterion 1:** the research presents no greater than minimal risk to the involved children **(45 CFR 46.404)**.

Inclusion/Exclusion Criteria: As there is no intervention as part of this registry, pregnant women and women of child-bearing potential will be included in this study.

Inclusion Criteria:

I One year of age and older
O Abdominal solid organ transplant recipient (kidney, liver, intestine) off immuno-suppression for at least 12 months
s Normal function of transplanted organ

Exclusion Criteria:

E Under one year of age
U Abdominal solid organ transplant recipient off immunosuppression less than 12 months
A Transplanted organ dysfunction

Recruitment Procedures: Collaborators will recruit subjects from their own patient populations. Each of the collaborating centers has been selected because they have expertise in solid organ transplantation and are active transplant centers. Each site will obtain written informed consent that is HIPAA compliant. As the collaborators will be recruiting from his/her own patient population, the investigator will explain the potential conflict of interest inherent in the dual role of physician/investigator by incorporating the following standard statements into the Right to Withdraw section of the consent form:

"Your doctor is involved as an investigator in this research study. As both your doctor and a research investigator, s/he is interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor."

All patients receiving care at one of the collaborating centers and who meet the inclusion/exclusion criteria will be invited to participate in the this registry. Potential participants will be approached by a collaborator who is also part of the clinical care team and will review the informed consent form with potential participants and address any questions or concerns prior to obtaining written informed consent.

Proxy Consent: Due to the small number of transplant recipients off immunosuppression, potential participants who are mentally incapacitated and therefore are unable to sign consent will be included in this study.

Any one of the following specific criteria will be used in determining whether the potential subject is incapacitated:
a)Glasgow coma scale of 14 or less
b)Intubated
c)Sedated by medications

The order in which persons are approached (depending on their availability) to sign the proxy consent is as follows:
1.Power of Attorney
2.Spouse who is 18 years or older
3.Off spring who is 18 years or older
4.Sibling who is 18 years or older

Consent to continue participation in the study will be part of the consent form. Once the subject regains cognition, his/her willingness to participate in the study will be reassessed. The section for continued participation in the informed consent will be completed by the subject before proceeding with the study.

Risk/Benefit Ratio: There are no risks of physical harm associated with participation in this registry. Participation in this study does involve the potential risks of a breach of confidentiality of the medical record information and associated privacy of the participants. Such risks will be minimized by 1) removing direct participant identifiers (i.e., names, social security numbers, medical record numbers) from information stored in the secure, web-based system; and 2) securing at each site, in a separate location, and limiting access to information linking study codes (i.e., linkage codes) with direct participant identifiers.

There are no direct benefits associated with participation in this registry. However, participation may lead to increased knowledge about tolerance in transplant patients. The use of information contained within the registry for retrospective research analyses may be of future benefit to organ transplant recipients. Participants in the registry will be informed of current and future research studies involving organ transplantation for which they may be eligible. This information will also be posted on the public and patient access portion of the web based system.

Data Safety and Monitoring Plan: This coordinating center registry will be reviewed yearly by the STI DSMB. The yearly IRB renewal for this study will include a summary report from the STI DSMB. In addition, a data and safety monitoring plan will be implemented by the Principal Investigator and the Coordinating Center Manager to ensure that there are no changes in the risk/benefit ratio during the course of the study and that confidentiality of research data is maintained. Collaborating centers will meet/participate in a teleconference at least yearly to discuss the study (e.g. goals, recruitment, data coding and analysis, documentation, adverse events, complaints, violations of confidentiality, etc) and address issues at that time. Also, the Principal Investigator, Coordinating Center Manager and the database manager will meet at least quarterly to discuss issues as above. If any issues or concerns arise at any time, they will be presented at the monthly STI DSMB meeting. Any instances of adverse events will be reported immediately to the University of Pittsburgh IRB using the standard forms and/or procedures that have been established by the IRB.

5. Costs and Payments
All costs associated with the implementation and maintenance of the web based registry shall be supported by the Thomas E. Starzl Transplantation Institute. Each study site will be responsible for any costs incurred as part of this study (i.e. investigator and/or coordinator time for IRB

preparation, consent process, entering data into web based system, etc). No costs will be incurred by participants. Participants will not be compensated for their participation.

Qualification of Investigators:

George Mazariegos, MD is an Associate Professor of Surgery and Director of Pediatric Transplantation and Children's Hospital of Pittsburgh. Dr. Mazariegos is very experienced in the management of patients following liver transplantation. He still follows some of the liver recipients who are adults now but were transplanted as children.

Fadi G. Lakkis, MD is a professor of Surgery and Immunology and Scientific Director of the Thomas E. Starzl Transplantation Institute at the University of Pittsburgh School of Medicine. In addition to his scientific and administrative roles, Dr. Lakkis is a transplant nephrologist with a 15-year experience in the inpatient and outpatient care of adult renal transplant recipients pre- and post-surgery. At UPMC, Dr. Lakkis will participate in the outpatient care of adult patients as part of the renal transplantation team.

Ron Shapiro, MD is a Professor of Surgery at the University of Pittsburgh School of Medicine and Director, Kidney, Pancreas and Islet Transplantation at the Thomas E. Starzl Transplantation Institute. He is very experienced in the management of patients following kidney transplantation. He helped to develop the use of the immunosuppressive agent tacrolimus (FK506) in adult and pediatric renal transplantation and is a leading expert in kidney transplantation.

Rakesh Sindhi, MD is an Associate Professor of Surgery and Director of Pediatric Transplantation Research at Children's Hospital of Pittsburgh. He performs liver and intestinal transplantation in children and has experience in research studies involving transplant patients.

Kareem Abu-Elmagd, MD, PhD is a Professor of Surgery at the University of Pittsburgh School of Medicine and Director, Intestinal Rehabilitation and Transplant Center at UPMC. He has extensive experience in managing small bowel transplant recipients.

Angus Thomson, PhD is a Professor of Surgery, Immunology and Molecular Genetics and Biochemistry with expertise in immunobiology, especially dendritic cell and T cell biology, and in the development of new immunosuppressive therapies.

Adriana Zeevi, PhD is a Professor of Pathology, Immunology and Surgery and the Director of the Tissue Typing Laboratory at UPMC. Dr. Zeevi has extensive experience with characterization of humoral alloimmune responses in transplant recipients. She has also been involved for over 20 years with post-transplant immune monitoring of solid organ transplant recipients.

Beth Elinoff, RN, MPH, CCRC is an experienced and certified clinical research coordinator. Ms. Elinoff has many years of experience coordinating investigator-initiated and federally-funded research studies, as well as managing coordinating centers. She is the Human Immunology Research Coordinator for the Thomas E. Starzl Transplantation Institute.

Michelle Nadler, APRN, BC is an experienced pediatric liver transplant nurse practitioner at St. Louis Children's Hospital. Ms. Nadler will assist in the management of the coordinating centers.

References: