ALLTOL

A Prospective Cohort Study of Operationally Tolerant Allograft Recipients

Protocol ITN063ST

Version 5.0 (September 4, 2019)

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This clinical study is supported and conducted by the Immune Tolerance Network, which is sponsored by the National Institute of Allergy and Infectious Diseases.

This document is confidential. It is provided for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. It is understood that the contents of this document will not be disclosed to others without written authorization from ITN and NIAID unless it is necessary to obtain informed consent from potential study participants.

Protocol Approval

Trial ID: ITN063ST	**Protocol Version:** 5.0
	Dated: September 4, 2019
IND # N/A	**Protocol Chair:** [redacted]
Title: ALLTOL: *A Prospective Cohort Study of Operationally Tolerant Allograft Recipients*	

I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of good clinical practice (GCP) as described in the US Code of Federal Regulations (CFR)—45 CFR part 46 and 21 CFR parts 50, 56, and 312, and in the International Conference on Harmonization (ICH) document Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance dated April 1996. Further, I will conduct the study in keeping with local legal and regulatory requirements.

As the principal investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without written permission of the NIAID.

_____

Principal Investigator **(Print)**

_____ _____

Principal Investigator **(*Sign*)** **Date**

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Synopsis

Title	ALLTOL: A Prospective Cohort Study of Operationally Tolerant Allograft Recipients
IND Sponsor	NIAID
Conducted by	Immune Tolerance Network
Protocol Chair(s)	[redacted]
Accrual Objective	There is no upper limit on the number of study participants, but we estimate that approximately 70 participants may be enrolled from former ITN studies and from de novo referrals.
Study Treatment	N/A
Study Design	This trial is a multi-center, prospective, observational study in which operationally tolerant recipients of liver or kidney allografts will be followed longitudinally with annual collections of clinical data and biological samples. All participants will be followed for the duration of the trial regardless of changes in their tolerance status. Participants will be recruited along three main pathways: 1. Tolerant participants from current and past ITN trials; including those who have already completed trial participation and those who are anticipated to complete trial participation; 2. Tolerant participants referred by ITN affiliated investigators, academic and community transplant physicians and directly through outreach to transplant affinity groups such as the National Kidney Foundation (NKF); 3. Tolerant participants from the general transplant community who are reachable through general media channels such as clinicaltrials.gov, the ITN website, word-of-mouth referrals from existing participants and social media. Participants will be encouraged to complete their study visits on site. However, participants who are unable or unwilling to travel to a study site will have the option of completing their study visits remotely (Figure 1).
Study Duration	The trial will continue through January 31, 2021.

Primary Objective

The primary objective of this study is to identify and longitudinally follow individuals who have received a kidney or liver transplant and who have achieved a state of operational tolerance to their allograft.

Operational tolerance is defined as meeting all of the criteria listed below:

1. Absence of biopsy-proven or clinical rejection, as determined by medical history
2. Maintenance off immunosuppressive medication, with the exception of short courses of steroids for non-allograft related conditions; e.g., asthma
3. Normal and stable allograft function (see Study Definitions). Allograft function tests used in primary endpoint calculations must be obtained in the absence of confounding factors. A Primary Endpoint Adjudication Committee (see Study Definitions) will review cases where confounding factors are suspected of having impact on the participant's test results and make recommendations toward resolution of the participant's status.

Primary Endpoint

The primary endpoint of this study is the time to loss of operational tolerance.

Secondary Endpoints

Safety

The following endpoints will be assessed for all participants:

1. Time to development of de novo anti-HLA antibody or DSA
2. Time to the first episode of biopsy-proven or clinical acute rejection, steroid resistant rejection and chronic rejection
3. Time to graft loss, not including death with functioning graft

Mechanistic

Mechanistic endpoints will longitudinally examine the following parameters with regard to operational tolerance:

4. Time course of changes in previously identified tolerance signatures in individual participants.
5. Expression levels for a wide variety of genes measured by large-scale microarray or by PCR assessments.
6. Flow-cytometric measurements of cell populations distinguished by cell-surface phenotype.
7. miRNA levels in peripheral blood
8. Gut microbiome profile

Inclusion Criteria

Participants must meet *all* of the following criteria to be eligible for this study:

1. Recipient of single organ liver or kidney allograft from a living or deceased donor.

2. At screening, operationally tolerant defined as meeting both of the following criteria:
   a. Absence of any immunosuppressive therapy for ≥ 52 weeks prior to the screening visit.
   b. No evidence of allograft rejection in the 52 weeks prior to the screening visit, based on the medical history.
3. Normal allograft function (see Study Definitions)

   If the site investigator judges that a participant exhibits stable allograft function despite values outside these criteria, then the participant is eligible if the ITN clinical trial physician/protocol chair, NIAID medical monitor and a subject matter expert concur.
4. Receiving regular follow up for a kidney or liver transplant by a local physician. Participants must be willing to allow the study team to contact and share medical information with this local physician.
5. Ability to sign informed consent.

Exclusion Criteria

Participants who meet any of the following criteria will *not* be eligible for this study:

1. Current malignancy requiring recent surgery, ongoing chemotherapy, or radiation.
2. Transplant of another organ.
3. Current drug or alcohol dependency.
4. Any medical condition that in the opinion of the principal investigator would interfere with safe completion of the trial.
5. Inability to comply with the study visit schedule and required assessments.

Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
CBC	complete blood count
CFR	Code of Federal Regulations
CKD	chronic kidney disease
CRF	case report form
CRO	contract research organization
DAIT	Division of Allergy, Immunology and Transplantation
DSMB	Data and Safety Monitoring Board
EDC	electronic data capture
FDA	US Food and Drug Administration
GCP	good clinical practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
HLA	human leukocyte antigen
ICH	International Conference on Harmonisation
IRB	institutional review board
ITN	Immune Tolerance Network
LFT	Liver function test
MSAP	mechanistic statistical analysis plan
MedDRA	Medical Dictionary for Regulatory Activities
MOP	manual of operations
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute *Common Terminology Criteria for Adverse Events* (version 4.3, June 10, 2010)

NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NKF	National Kidney Foundation
PBL	peripheral blood lymphocytes
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	pharmacodynamics
PTLD	Post-transplant lymphoproliferative disorder
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse event
SACCC	Statistical and Clinical Coordinating Center
SOE	schedule of events
STS	Specimen Tracking System
TCR	T-Cell Receptor
ULN	upper limit of normal
WHO	World Health Organization

Study Definitions Page

Adverse Event	Any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (Section 8.2.1).
Biliary Complications	Incidence of biliary complications including any of the following: • Biliary stricture requiring stenting • Other evidence of biliary obstruction • Cholangitis
Enrollment	The signing of informed consent (Section 3.1.1).
Liver Graft Loss	The incidence of any of the following: • Re-transplantation • Re-listing for transplantation • Participant death with a non-functioning graft
Normal and stable graft function	**Baseline (Values collected at screening):** Liver transplant recipients: Liver function tests (ALT, GGT) both less than or equal to the upper limit of normal (ULN). Kidney transplant recipients: Serum creatinine value correspond to an estimated GFR > 45 ml/min/1.73 m^2. **Post-Baseline** Liver function tests (ALT, GGT) (for liver transplant recipients) that have not increased more than 50% above the participant's baseline values or serum creatinine (for kidney transplant recipients) that have not increased more than 25% above the participant's baseline values, and these tests were collected in the absence of confounding factors.
Operational Tolerance	Participants must meet all of these criteria for at least 52 weeks after the last documented dose of immunosuppressive medication: 1. Absence of rejection (biopsy-proven or clinical rejection) 2. Maintenance off immunosuppressive medication 3. Normal and/or stable allograft function
Primary Endpoint Adjudication Committee	The Primary Endpoint Adjudication Committee is comprised of the Study Protocol Chair/ITN Clinical Trial Physician, NIH Medical Monitor, a subject matter expert, and Statistician. The Committee will review the participant's clinical history to determine whether the participant is operationally tolerant.
Renal Function	Estimated GFR calculated for adults by CKD-EPI and for pediatric participants (<18 years) by both CKD-EPI and modified Schwartz formulae[1].
Renal Graft Loss	The incidence of any of the following: • Institution of chronic dialysis (at least 6 consecutive weeks) • Transplant nephrectomy • Re-transplantation • Re-listing for transplantation
Serious Adverse Event	Any adverse event that meets one or more serious criterion and occurs within 24 hours of the protocol mandated blood draw for research specimens. Events that occur outside the 24 hour period that meet serious criteria should be reported if the site investigator deems a possible or definite association with a protocol mandated blood draw (Section 8.2.3).

Time Zero	Defined as 52 weeks from the participant's last documented dose of immunosuppression and in the absence of rejection or evidence for loss of normal and stable graft function since that last dose.
Upper Limit of Normal (ULN)	ULN values will be defined by age appropriate ranges from Harrison's Principles of Internal Medicine, 18th edition (Appendix 2) or Harriet Lane Handbook, 19th edition (Appendix 3).

1. BACKGROUND AND RATIONALE

1.1 BACKGROUND

Life-long immunosuppression is typically regarded as obligatory for solid-organ recipients to avoid the risk of graft loss from alloimmune attack. Evidence that not all patients require perpetual immunosuppression to maintain their graft is found in a small subset of patients who successfully discontinue immunosuppression through non-compliance or out of medical necessity (i.e. PTLD), and yet sustain normal graft function apparently indicating a state of operational tolerance. For kidney, this fraction is estimated at ~5-10%[2]. For liver it has traditionally been estimated at 20%[3,4]. However recent studies demonstrate that the prevalence of operational tolerance may be as high as 40% in adult liver recipients and as high as 60% in a highly selected cohort of pediatric liver recipients[5,6].

Longitudinal study of an operationally tolerant cohort will allow us to assess the durability of the tolerance phenotype, the effect of allograft subtype on the maintenance of tolerance and potential triggers associated with breaking of tolerance. Study of these patients might provide clues to tolerance mechanisms, thereby facilitating its prospective replication in non-spontaneously tolerant recipients. Finally the study of these patients may allow us to identify and validate biomarkers predictive of the tolerant phenotype.

1.2 SCIENTIFIC RATIONALE

Recent studies suggest that gene expression analysis in peripheral blood and/or urine lymphocytes may identify the immune status of the graft. Gene signatures predicting rejection in heart and kidney recipients[7-11] and a state of functional tolerance in liver and kidney patients[12-14] have been identified. In the kidney setting, Newell et al made the unexpected observation in a cross-sectional analysis of operationally tolerant renal transplant recipients that tolerance was associated with an expression signature dominated by B cell transcripts[12]. A three gene set validated by PCR was found to have high positive and negative predictive value. Interestingly, each of the three genes was involved in B cell maturation and development. These molecular signals were confirmed in PBL flow analysis which revealed parallel B cell subset differences with expansion of immature stage B cells that correlated with tolerance. Of note, the kidney signature identified by Newell has not yet been validated by a prospective weaning trial.

In the liver transplant setting, Martinez-Llordella *et al* studied 16 operationally tolerant liver recipients by PBL transcriptional profiling and detailed flow subset characterization and compared them to 16 patients on immunosuppression and 10 normal controls. A gene expression signature indicative of tolerance was identified that included genes encoding γδT cells and NK cells. By flow there was an increase in the Treg subset[13]. An attempt was recently undertaken to validate these findings prospectively in a multicenter trial by weaning from immunosuppression. The trial's molecular signature analysis published in JCI in 2012 revealed a robust tissue signature unexpectedly dominated by transcripts associated with iron metabolism[15].

Establishment of a prospective cohort study of tolerant patients will allow cross-validation of these and other signatures as well as discovery of *de novo* signatures associated with tolerance.

1.3 SUMMARY OF KNOWN AND POTENTIAL RISKS AND BENEFITS FOR HUMAN PARTICIPANTS

1.3.1 Risks

1.3.1.1 Risks associated with Blood Draws

Risks to participants will be limited to collection of biological samples every year. During these collections, participants may experience some discomfort, minor bruising, or fainting during blood collection. There is also a very small chance (less than 1%) of infection at the needle puncture site.

1.3.2 Benefits

Participation in this trial will not result in any direct benefit, however, the information gathered during this study may someday be of benefit to transplant recipients.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to identify and longitudinally follow individuals who have received a kidney or liver transplant and who have achieved a state of operational tolerance to their allograft. Operational tolerance is defined as meeting all three and loss of operational tolerance is defined as failing to meet any one of the following criteria:

1. Absence of rejection (biopsy-proven or clinical rejection), as determined by medical history
2. Maintenance off immunosuppressive medication, with the exception of short courses of steroids for non-allograft related conditions; i.e. asthma
3. Normal and stable allograft function (see Study Definitions). Allograft function tests used in primary endpoint calculations must be obtained in the absence of confounding factors. A Primary Endpoint Adjudication Committee (see Study Definitions) will review cases where confounding factors are suspected of having impact on the participant's test results and make recommendations toward resolution of the participant's status.

2.2 SECONDARY OBJECTIVES

1. To create an electronic database of operationally tolerant allograft recipients.
2. To create a repository for samples obtained from operationally tolerant allograft recipients.
3. To assess the durability of operational tolerance in allograft recipients over time.
4. To analyze changes over time in previously identified biomarkers predictive of or associated with operational tolerance in allograft recipients.
5. To follow markers of immunologic activity over time for possible use in exploratory biomarker analysis.

2.3 EXPLORATORY OBJECTIVE

To assess the medical outcomes of operational tolerance over time, as determined by medical history, in allograft recipients.

3. STUDY DESIGN

3.1 DESCRIPTION

This trial is a multi-center, prospective, observational study in which operationally tolerant recipients of liver or kidney allografts will be followed longitudinally with annual collections of clinical data and biological samples. All participants will be followed for the duration of the trial regardless of changes in their tolerance status.

Participants will be recruited along three main pathways:

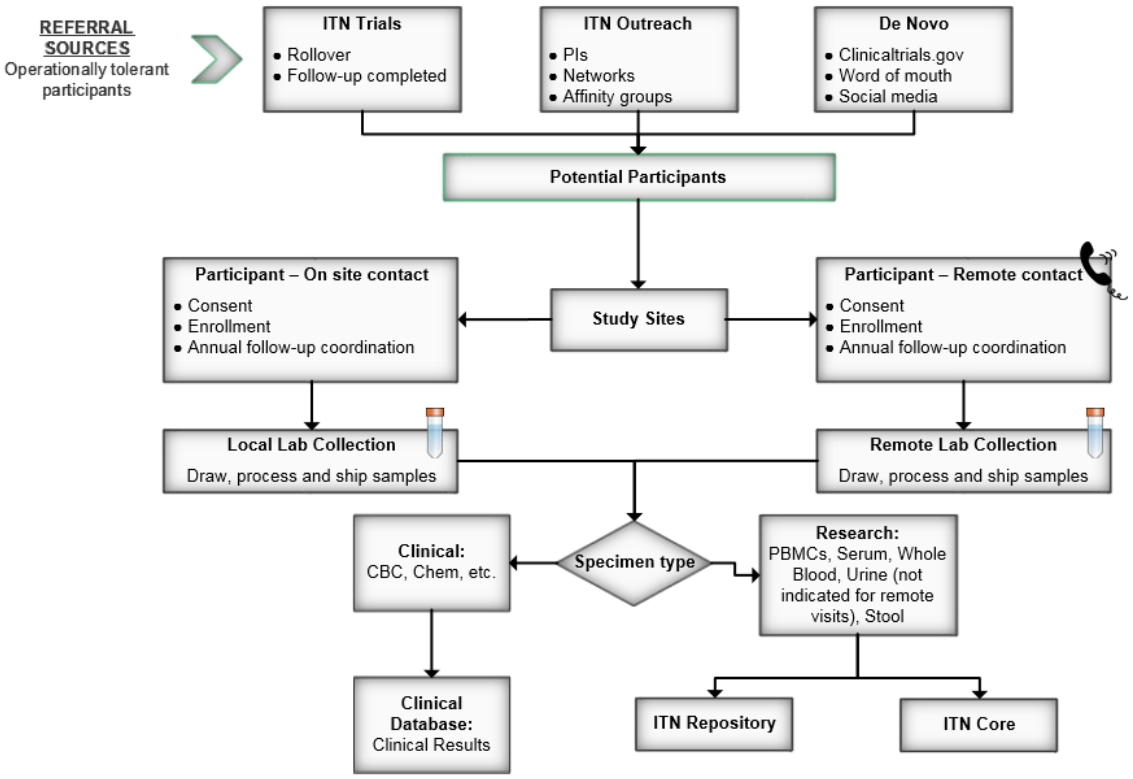
1. Tolerant participants from current and past ITN trials; including those who have already completed trial participation and those who are anticipated to complete trial participation;

2. Tolerant participants referred by ITN affiliated investigators, academic and community transplant physicians and directly through outreach to transplant affinity groups such as the National Kidney Foundation (NKF);

3. Tolerant participants from the general transplant community who are reachable through general media channels such as clinicaltrials.gov, the ITN website, word-of-mouth referrals from existing participants and social media.

Participants will be encouraged to complete their study visits on site. However, participants who are unable or unwilling to travel to a study site will have the option of completing their study visits remotely (Figure 1).

Figure 1. Schematic of Study Conduct



3.1.1 Recruitment Plan

This initiative will be publicized at national and international meetings that focus on liver and kidney transplantation using announcements included in the scientific program. Materials will also be distributed at the national and regional meetings of organizations such as the National Kidney Foundation (NKF) and Juvenile Diabetes Foundation (JDF) that have a major involvement with liver and kidney transplantation. Announcements will also be included in the newsletters of the aforementioned organizations. This project will also be advertised in major transplant journals (i.e., *American Journal of Transplantation*, *Transplantation*, *Clinical Transplantation,* etc.) and on the web pages of the ITN, National Institutes of Health (NIH), JDF, NKF, American Society of Transplantation (AST), American Society of Transplant Surgeons (ASTS), and the Transplantation Society. All advertisement materials will receive appropriate IRB/EC approval.

The medical and surgical directors of all major liver and kidney transplant programs will also be contacted by mail, telephone and e-mail in an attempt to locate tolerant participants. These contacts will also include investigators from previous ITN liver and kidney transplant trials who have enrolled and followed tolerant participants. A potential candidate's primary care physician may inform him/her of the study and if the potential candidate is interested in learning more about the study he/she may contact the study investigator. These primary care physicians will also be

provided with an IRB/EC approved "Dear Patient" letter describing the study and providing key contact information, which includes the internet address of a web page that outlines the trial and allows entry of basic information that will be used as a preliminary screening tool. Furthermore, traditional contact information (telephone, fax numbers, and email address) will also be provided.

Study candidates who have participated in previous ITN studies will be first contacted by a physician at their prior ITN study site notifying them of the ALLTOL study. Interested candidates will be instructed to contact ALLTOL study sites. Study candidates who have not previously participated in an ITN study will be identified through referral by their physician or the ALLTOL study recruitment website.

3.1.2 Enrollment and Accrual

Enrollment will occur on an ongoing basis through November 1, 2020. There is no upper limit on the number of study participants, but we estimate that approximately 70 participants may be enrolled from former ITN studies and from de novo referrals. Enrollment is defined as the signing of informed consent and will be obtained prior to the initiation of any screening or study mandated procedures. Enrolled participants who do not fulfill eligibility criteria or who do not complete any mechanistic sample collection for any reason will be considered screen failures. Screening values will be considered the participant's baseline for those who meet all eligibility criteria. If a repeat assessment is needed to confirm eligibility, the repeat value will be considered the participant's baseline value. There is no upper limit on screen failures.

3.1.3 Screen Failures

Screening data will be collected on all participants who have signed informed consent and undergone screening but who fail to meet eligibility criteria or who do not complete any mechanistic sample collection for any reason. The reasons for ineligibility will be tabulated.

3.2 STUDY DURATION

The trial will continue through January 31, 2021.

3.3 STUDY ENDPOINTS

3.3.1 Timing of endpoints and subsets for analysis of endpoints

Study endpoints for all participants will be evaluated relative to Time Zero. Time Zero will be considered the time that operational tolerance was obtained prior to study entry (see Study Definitions). If the exact date of the last dose is not known, the date will be imputed to the 15th of the month when the day is missing, and July 1st when both day and month are missing. The year must be known.

The following subset analyses will be performed on all study endpoints:

a. allograft type (i.e.- liver or kidney)

b. previous ITN study participation or non-ITN study-referral

3.3.2 Primary Endpoint

The primary endpoint of this study is the time to loss of operational tolerance.

3.3.3 Secondary Endpoints

Safety
The following endpoints will be assessed for all participants:

1. Time to development of de novo anti-HLA antibody or DSA
2. Time to the first episode of biopsy-proven or clinical acute rejection, steroid resistant rejection and chronic rejection
3. Time to graft loss, not including death with a functioning graft

Mechanistic
Mechanistic endpoints will longitudinally examine the following parameters with regard to operational tolerance:

4. Time course of changes in previously identified tolerance signatures in individual participants
5. Expression levels for a wide variety of genes measured by large-scale microarray or by PCR assessments
6. Flow-cytometric measurements of cell populations distinguished by cell-surface phenotype
7. MiRNA levels in peripheral blood
8. Gut microbiome profile

3.3.4 Exploratory Endpoints

1. Time to all-cause mortality
2. Changes in renal function (defined as estimated GFR calculated for adults by CKD-EPI and for pediatric participants (< 18 years) by both CKD-EPI and modified Schwartz formulae) over time in renal transplant recipients[1]
3. Changes in liver tests (ALT, GGT) over time in liver transplant recipients
4. Time to incidence of biliary complications in liver transplant recipients
5. Incidence of diabetes or use of concomitant medications for hypertension and/or hyperlipidemia

3.4 PREMATURE TERMINATION OR SUSPENSION OF THE TRIAL / STOPPING RULES

There will be no stopping rules for this trial.

4. ELIGIBILITY

4.1 INCLUSION CRITERIA

Participants must meet *all* of the following criteria to be eligible for this study:

1. Recipient of single organ liver or kidney allograft from a living or deceased donor.
2. At screening, operationally tolerant defined as meeting both of the following criteria:
   a. Absence of any immunosuppressive therapy for ≥ 52 weeks prior to the screening visit.
   b. No evidence of allograft rejection in the 52 weeks prior to the screening visit, based on the medical history.
3. Normal allograft function (see Study Definitions)

   If the site investigator judges that a participant exhibits stable allograft function despite values outside these criteria, then the participant is eligible if the ITN clinical trial physician/protocol chair, the NIAID medical monitor and a subject matter expert concur.
4. Receiving regular follow-up for a kidney or liver transplant by a local physician. Participants must be willing to allow the study team to contact and share medical information with this local physician.
5. Ability to sign informed consent.

4.2 EXCLUSION CRITERIA

Participants who meet any of the following criteria will *not* be eligible for this study:

1. Current malignancy requiring recent surgery, ongoing chemotherapy, or radiation.
2. Transplant of another organ.
3. Current drug or alcohol dependency.
4. Any medical condition that in the opinion of the principal investigator would interfere with safe completion of the trial.
5. Inability to comply with the study visit schedule and required assessments.

4.3 PREMATURE TERMINATION OF A PARTICIPANT FROM THE STUDY

Withdrawal of consent. Participants who withdraw consent for further follow-up.

Investigator decision. The principal investigator may choose to withdraw a participant from the study for any reason.

Failure to return. Participants who do not return for visits and who do not respond to repeated attempts by the site staff to have them return will be considered *lost to follow-up*.

Participants who prematurely terminate from the study will not be replaced.

5. STUDY MEDICATIONS

5.1 INVESTIGATIONAL MEDICATION

This section left intentionally blank.

5.2 CONCOMITANT MEDICATIONS

All immunosuppressive medications and any concomitant medications taken within 30 days prior to enrollment and to each annual visit will be documented at each visit. There are no prohibited medications.

6. STUDY PROCEDURES

Study procedures will be limited to yearly venipuncture and urine for clinical labs and mechanistic sample collection. A stool sample will also be acquired yearly for mechanistic purposes.

6.1 VISIT WINDOWS

6.1.1 Scheduled Visits

Appendix 1 presents the schedule of events for this trial. Visit 0 must occur within 60 days of enrollment. All other scheduled study visits must occur within ±60 days of the scheduled time point listed in Appendix 1.

6.2 GENERAL ASSESSMENTS

Recipient

- Informed consent
- Medical and demographic history including solid organ transplant specifics, any induction regimens, history of rejection and immunosuppression medication use since transplant:
    - For participants who previously participated in an ITN study, the participant ID and site ID (if separate) will be collected on the ALLTOL eCRF. The participant ID will be obtained by asking the ALLTOL participant for their previous ITN study participant ID and clinical study site.
- Contact information for local physician providing regular follow-up care for the kidney or liver transplant. Local care providers will be notified of any critical clinical information that may indicate allograft dysfunction. This process is further outlined in the MOP.
- Inclusion/Exclusion Criteria
- HLA and blood typing (if available)
- Change in adverse events and concomitant medications
- Development of clinical outcomes of interest, which include incidence of diabetes and/or any biliary complications

- If there is a 25% increase in the value(s) collected during the scheduled annual visit compared to the participant's baseline value, collect all liver function tests (for liver transplant recipients) or all serum creatinine levels (for kidney transplant recipients) since the last visit
- All biopsies
- All rejection episodes, including acute rejection, chronic rejection, antibody mediated rejection, and interstitial fibrosis and tubular atrophy rejection episodes

Donor

- Donor type (living-related donor, living-unrelated donor, deceased-donor)
- Demographics
- HLA and blood typing (if available)

6.3 CLINICAL LABORATORY ASSESSMENTS

These laboratory assessments may be performed at study sites, at local laboratories, or though the central laboratory:

- Hematology – CBC with differential and platelets
- Comprehensive Metabolic Panel (Na, K, Cl, HCO3, BUN, creatinine, calcium, glucose, albumin, total bilirubin, direct bilirubin, GGT, AST, ALT, and alkaline phosphatase)
    - Screening allograft function tests must be obtained in the absence of confounding factors such as dehydration, infection etc. Abnormal test results should be repeated to confirm eligibility after any confounding conditions have resolved.
- Fasting lipid panel
- Urine albumin-creatinine ratio
- Urinalysis (protein, glucose, WBC, and hematuria)

6.4 MECHANISTIC ASSESSMENTS

- Frozen PBMC – flow cytometry panel staining
- Frozen PBMC – cellular assays
- Serum – HLA alloantibodies, includes DSA, flow PRA
- Whole Blood – RNA gene expression profiling
- Urine pellet – gene expression profiling (not indicated for remote visits)

- Fecal – microbiome profiling

See section 7 for detailed discussion of additional mechanistic assays.

7. TOLERANCE ASSAYS

7.1 MECHANISTIC STUDIES

The aim of this trial is to create a repository for samples obtained from operationally tolerant transplant recipients that have either completed ITN studies or have otherwise successfully withdrawn from immunosuppressive therapy. These samples will allow the ITN to longitudinally assess the phenotype, maintenance, generation, and stability of immune transplant tolerance in both kidney and liver transplant recipients. In addition, mechanistic data and samples collected from ALLTOL participants during previous ITN studies may be used to supplement the ALLTOL specimens and data, as needed.

We propose to monitor related parameters over time and collect blood, cells, serum, urine, urine pellet, and fecal microbiome samples from tolerant participants. As the field of tolerance is evolving, markers of interest will be determined based on the literature and state-of-the-art at the time of experimentation.

7.2 FUTURE / UNPLANNED STUDIES

Exploratory ancillary studies may be performed at a future date. Appropriate comparator arms will be determined at the time of experimentation and may include comparison with previously banked specimens or recruitment of control participants. Participants will be consented for sample storage and future use. Specimens stored during the trial may also be used in future assays to reevaluate biological responses as research tests are developed over time. Additionally, samples may be used for assays/ experiments outside the scope of this proposal, such investigation of miRNA expression, differences in the TCR repertoire as evaluated by sequencing, proteomics or other explorations that may emerge and be compelling during the trial period. Reevaluations or new assays will only be performed on samples of participants who have consented for future research. Blood samples will be collected and saved to allow for the possible use in later gene association studies. Specific consent will be obtained for the storage and use of participant DNA. The ITN sample sharing policy will apply for the provision of samples to study or outside investigators.

7.3 SPECIMEN LOGISTICS

Sites will be trained in the collection, processing, shipment, and tracking of mechanistic research specimens. The ITN will monitor specimen quality, shipping compliance, etc., and retrain any clinical site that is not producing optimum quality mechanistic samples. Sites will process all mechanistic samples according to the ITN standard procedures and use the ITN Specimen Tracking System (STS) software to identify and track all mechanistic specimens. The sites will be required to have certain laboratory equipment for use in following ITN procedures, such as a centrifuge for spinning primary blood tubes, a micropipettor to aliquot specimens, and freezer to store frozen specimens until they can be shipped. Sites will use appropriate courier service for shipping specimens to repositories/ core labs, per ITN standard procedures. All shipping will

conform to Department of Transportation regulations (49 CFR 173.199) for Diagnostic Specimens.

If samples cannot be collected at the study site, the site study coordinator will arrange for a representative from an ITN approved vendor to come to the participant's location to complete the study assessments. The ITN approved vendor will be trained in the ITN standard procedures for collection, processing and shipment of mechanistic research specimens. The site study coordinator(s) will use the ITN Specimen Tracking System (STS) software to identify and track all mechanistic specimens.

7.3.1 Specimen Tracking Procedures

The ITN will track all mechanistic specimens until the final disposition of all material is known. Samples will remain in the ITN repository until used for assays or destroyed.

7.3.2 Sample Storage

Samples sent to the ITN repository will be stored under specific conditions to maintain long-term sample integrity, as well as specimen tracking from receipt to shipment to alternate locations. A 21 CFR Part 11 validated database system can be used to track shipment date, location shipped to, carrier, items shipped, amount shipped, barcode numbers, protocol number, and associated comments about each individual specimen. Storage temperature, location, processing and aliquoting, and freeze/thaw events may also be recorded.

If the study participant allows storage, the participant's specimens will be stored indefinitely. The participant can change their mind at any time and have their stored specimens destroyed by notifying the study physician in writing. In such cases, the site coordinator would send all requests for sample destruction to the ITN. The site will receive confirmation that the specimen was destroyed as requested. If the participant's samples have already been analyzed, then the data will be used as part of the overall analysis. The participant can only request to have samples destroyed if they still exist, i.e. have not already been used in an experiment.

Specimens at the ITN core or repository can only be transferred to another destination with appropriate authorization per ITN standard procedures. Purpose for accessing/transferring the specimen (within study assay as defined by the protocol or future studies), evaluation of participant consent for the purpose provided, verification of specimen identifiers, and quality and quantity of the specimen are some of the items checked prior to authorization.

If the purpose is for future studies, and the participant consents for storage for future use, the participant's sample may be made available to the scientific research community per the ITN Sample Sharing Policy [redacted] Any research conducted using stored samples for future use may also need appropriate regulatory approval, such as Institutional Review Board per the study consent.

8. SAFETY MONITORING

8.1 OVERVIEW

This study involves minimal intervention outside of the normal standard of care of the participant. For this study, "reportable" is used to denote "reportable" to the Institutional Review Board

(IRBs)/Ethics Committee (EC), Data Safety Monitoring Boards (DSMBs), and the study sponsor (NIAID).

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events that are classified as serious according to the definition of health authorities must be reported promptly to the sponsor DAIT/NIAID or other Sponsor. Appropriate notifications will also be made to site principal investigators, Institutional Review Boards (IRBs) and health authorities.

Information in this section complies with ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice, 21CFR Parts 312 and 320, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0: http://ctep.cancer.gov/reporting/ctc.html.

For this study, reportable adverse events will be limited to those that meet one or more serious criteria and occur within 24 hours of the protocol-mandated blood draw. In addition, events that occur outside the 24 hour period that meet serious criteria will be reported if the site investigator deems a possible or definite association with a protocol mandated blood draw. The NIAID medical monitor will review each SAE and assess the relationship of the event to the study procedure.

8.2 DEFINITIONS

8.2.1 Adverse Event

Any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)" http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2).

Only adverse events meeting serious criteria will be collected for this study (see Section 8.4).

8.2.2 Suspected Adverse Reaction (SAR)

Any adverse event for which there is a reasonable possibility that the investigational drug [or investigational study therapy regimen] caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

We do not anticipate any reported SARs since this study is observational and there is no protocol specific study therapy regimen.

8.2.3 Serious Adverse Event

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Sponsor (DAIT/NIAID), it results in any of the following outcomes (21 CFR 312.32(a)):

1. Death.
2. A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the investigator or DAIT/NIAID, its occurrence places the subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly or birth defect.
6. Important medical events that might not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they might jeopardize the subject and might require medical or surgical intervention to prevent one of the outcomes listed above.

For this study, a SAE is defined as "any adverse event that meets one or more serious criterion and occurs within 24 hours of the protocol mandated blood draw for research specimens." In addition, events that occur outside the 24 hour period that meet serious criteria should be reported if the site investigator deems a possible or definite association with a protocol mandated blood draw.

The NIAID medical monitor will review each SAE and assess the relationship of the event to the study procedure.

8.3 GRADING AND ATTRIBUTION OF SERIOUS ADVERSE EVENTS

8.3.1 Grading Criteria

The study site will grade the severity of serious adverse events experienced by the study subjects that meet the study reporting criteria described in section 8.2 (above). SAEs will be graded according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE – Version 4.0) for all adverse events. This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. The NCI-CTCAE has been reviewed by the study investigator and has been deemed appropriate for the subject population to be studied in this protocol for all adverse events.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

a. Grade 1 = mild adverse event.

b. Grade 2 = moderate adverse event.

c. Grade 3 = severe and undesirable adverse event.

d. Grade 4 = life-threatening or disabling adverse event.

e. Grade 5 = death.

Serious Adverse Events grading will be recorded on the appropriate SAE case report form. If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an adverse event if changes in therapy or monitoring are implemented as a result of the event/result.

8.3.2 Attribution Definitions

The relationship, or attribution, of a serious adverse event to a study-mandated blood draw will initially be determined by the site investigator and recorded on the appropriate SAE CRF. Final determination of attribution will be determined by DAIT/NIAID. The relationship of an adverse event to study intervention will be determined using the descriptors and definitions provided in Table 1. Attribution of Serious Adverse Events.

Table 1. Attribution of Serious Adverse Events

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy or study procedure.
Unrelated Category		
1	Unrelated	The adverse event is clearly not related.
Related Categories		
2	Possible	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Definite	The adverse event is clearly related.

8.4 COLLECTION AND RECORDING OF SERIOUS ADVERSE EVENTS

8.4.1 Collection Period

Serious adverse events will be collected from the time of first study blood draw until 30 days after the subject prematurely withdraws (without withdrawing consent), is withdrawn from the study, or completes the study.

8.4.2 Collecting Serious Adverse Events

Only adverse events that meet serious criteria will be collected for this study. A SAE that occurs within 24 hours after a protocol-mandated blood draw must be reported for this study. In addition, events meeting serious criteria that occur more than 24 hours after a protocol mandated blood

draw must be reported if the site investigator deems a possible or definite association with a protocol mandated blood draw. Such events can include, but are not limited to:

- Infection at the phlebotomy site or infections where the phlebotomy site in considered a possible portal of entry.
- Significant hemorrhage or bruising at the phlebotomy site.
- Fainting associated with the phlebotomy procedure resulting in further injury.
- Events meeting serious criteria that occur outside the 24 hour time parameters or are not listed above should be reported if the investigator deems a possible association with the protocol mandated blood draw for research specimens.

Serious Adverse events may be discovered through any of the following methods:

- Reviewing the information in the subject's medical chart.
- Interviewing the subject (e.g., using a checklist, structured questioning, diary, etc.)
- Receiving an unsolicited complaint from the subject.

In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate a serious adverse event, as defined in Section 8.3, Grading and Attribution of Serious Adverse Events.

8.4.3 Exceptions to Collection

Non-study-related events should be reported only when they occur within 24 hours of a protocol mandated blood draw and meet serious criteria. (Please see Section 8.2.3, Serious Adverse Event).

8.4.4 Recording Adverse Events

Throughout the study, the investigator will record serious adverse events as described previously (Section 8.2, Definitions) on the appropriate AE/SAE form regardless of the relationship to study procedure.

Once recorded, a serious adverse event will be followed until it resolves with or without sequelae, until the end of study participation, or until 30 days after the subject prematurely withdraws (without withdrawing consent) /or is withdrawn from the study, whichever occurs first.

8.5 REPORTING OF SERIOUS ADVERSE EVENTS

8.5.1 Reporting of Serious Adverse Events to Sponsor (DAIT/NIAID)

This section describes the responsibilities of the site investigator to report serious adverse events to the sponsor via the SACCC eCRF. Timely reporting of adverse events is required by 21 CFR and ICH E6 guidelines.

Site investigators will report all serious adverse events (see Section 8.2.2, Serious Adverse Event), regardless of relationship or expectedness within 24 hours of discovering the event.

For serious adverse events, all requested information on the AE/SAE form should be provided. However, unavailable details of the event will not delay submission of the known information. As additional details become available, the adverse event / serious adverse event should be updated and submitted.

8.5.2 Reporting of Adverse Events to IRBs/IECs

All investigators shall report serious adverse events in a timely fashion to their respective IRBs/IECs in accordance with applicable local regulations and guidelines.

8.6 PREGNANCY REPORTING

As no investigational agents or procedures are required in this study, pregnancies will not be recorded or considered a reportable serious adverse event.

8.7 REPORTING OF OTHER SAFETY INFORMATION

An investigator shall promptly notify the site IRB as well as the SACCC when an "unanticipated problem involving risks to subjects or others" is identified, which is not otherwise reportable as a serious adverse event.

8.8 REVIEW OF SAFETY INFORMATION

8.8.1 Medical Monitor Review

The DAIT/NIAID Medical Monitor shall receive monthly reports from the SACCC compiling new and accumulating information on SAEs recorded by the study sites on appropriate eCRFs.

In addition, the Medical Monitor shall review and make decisions on the disposition of the SAE reports received by the SACCC (See Section 8.5.1, Reporting of Serious Adverse Events to Sponsor).

8.8.2 DSMB Review

8.8.2.1 Ad hoc DSMB Reviews

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for ad hoc reviews. The DSMB will review any event that potentially impacts safety at the request of the principal investigator and/or the DAIT/NIAID medical officer.

After careful review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

9. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

9.1 ANALYSIS SAMPLE

The analysis sample will be comprised of all enrolled subjects that fulfill eligibility criteria and complete at least one mechanistic sample collection. Furthermore, clinical data and mechanistic specimens that have already been collected from enrolled subjects from previous ITN study participation may be used to supplement the ALLTOL specimens and data, as needed.

In addition, the following subset analyses will be performed on all study endpoints:

a. allograft type (liver vs kidney)

b. previous ITN study participation vs non-ITN study-referral

9.2 ANALYSIS PLAN

9.2.1 Primary Endpoint

The primary endpoint is defined in section 3.3.2.

A confounding factor may prevent measurement of normal and stable allograft function. Participants who return to normal and stable allograft function after resolution of the confounding factor and who otherwise meet the primary endpoint criteria will be adjudicated by a Primary Endpoint Adjudication Committee (see Study Definitions).

The primary endpoint will be analyzed using Kaplan-Meier survival estimates and associated two-sided 95% confidence intervals, using a delayed-entry model controlling for left-truncation of survival times through adjusting for the time from achieving operational tolerance to the time of study enrollment. A participant will be considered to have lost operational tolerance if they experience rejection, have loss of stable allograft function (in the absence of confounding factors), or restart immunosuppression. The date of loss of operational tolerance will be the first date on which the subject meets any of the criteria for loss of operational tolerance. Subjects lost to follow-up will be censored at the time of occurrence of the event causing their loss to follow-up.

9.2.2 Secondary Endpoints

The secondary endpoints are defined in section 3.3.3.

- Proportion endpoints will be descriptively summarized using frequency tables with frequencies and percentages and 95% exact binomial confidence intervals.
- Time-to-event endpoints will be assessed using Kaplan-Meier survival estimates and associated two-sided 95% confidence intervals from a delayed-entry model as described for the primary analysis. Statistical methods for interval-censored data will be applied for endpoints with unknown exact dates. Subjects who are lost to follow-up will be censored at the time of occurrence of the event. Furthermore, participants who lose operational tolerance will continue to be followed for the duration of the study. These participants

will be considered to have lost operational tolerance on the date of loss of stable allograft function (in the absence of confounding factors), reinitiation of immunosuppression or diagnosis of rejection, whichever comes first.

- Continuous endpoints will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, maximum).
- Categorical variables will be summarized using counts (n) and percentages (%).

9.2.3 Description of Baseline Characteristics and Demographics

Demographic and baseline characteristic data will be summarized with descriptive statistics (n, mean, standard deviation, median, minimum, and maximum for continuous variables; counts and percents for categorical variables).

9.2.4 Medical History

Medical history will be collected, including the existence of past and current chronic medical conditions, sensitization information (including previous transplants and cause of primary allograft loss), primary records for the transplant procedure (including donor source, cadaveric or living), and post-transplant evaluation and management (including initial immunosuppressive agents used, episodes of allograft dysfunction, and discontinuation of immunosuppressive agents).

9.2.5 Use of Medications

Medication use per section 5.2 and all immunosuppressive medication use will be collected.

9.2.6 Study Completion

The percent of participants who fail to complete the study, losses to follow-up, times to loss to follow-up, and reasons for discontinuation (AEs, other) will be presented.

9.2.7 Adverse Events

AEs and SAEs will be summarized using frequencies and proportions.

9.3 SAMPLE SIZE

This is a prospective cohort trial with an objective to collect as many tolerant subjects together with their biological samples as possible. There is no minimum sample size, and all eligible subjects will be enrolled through January 31, 2021. We estimate that approximately 70 participants may be enrolled from former ITN studies and from de novo referrals through 2021.

9.4 REPORTING DEVIATIONS FROM THE ORIGINAL STATISTICAL PLAN

There will be no statistical analysis plan prepared for this exploratory study, but all analyses will be described in the final study report as appropriate.

10. ACCESS TO SOURCE DATA/DOCUMENTS

The investigational sites participating in this study will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from participants in this clinical trial. Medical and research records should be maintained at the investigational sites in the strictest confidence. However, as a part of the quality assurance and legal responsibilities of an investigation, the investigational sites must permit authorized representatives of the ITN, sponsor, and health authorities to examine (and to copy when required by applicable law) 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 (and any personally identifying information must be obscured). 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 sites will normally be notified in advance of auditing visits.

11. QUALITY CONTROL AND QUALITY ASSURANCE

The principal investigator is required to keep accurate records to ensure that the conduct of the study is fully documented. The principal investigator is required to ensure that all eCRFs are completed for every participant entered in the trial.

The sponsor is 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.

The eCRFs will be completed online via a web-based electronic data capture (EDC) system that has been validated and is compliant with Part 11 Title 21 of the Code of Federal Regulations. Some data requirements will be addressed outside the EDC using SAS® software. Data queries will be issued and resolved within the EDC system or SAS®.

Study staff at the sites will enter information into the electronic CRFs, and the data will be stored remotely at a central database. Data quality will be ensured through the EDC system's continuous monitoring of data and real-time detection and correction of errors. All elements of data entry (i.e., time, date, verbatim text, and the name of the person performing the data entry) will be recorded in an electronic audit trail to allow all changes in the database to be monitored and maintained in accordance with federal regulations.

Study staff will enter data from a study visit on the relevant eCRFs within 3 days following the visit or the time when data become available.

12. ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

12.1 STATEMENT OF COMPLIANCE

This trial will be conducted in compliance with the protocol, current Good Clinical Practice (GCP) guidelines—adopting the principles of the Declaration of Helsinki—and all applicable regulatory requirements.

Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by the sponsor and an appropriate ethics review committee or institutional review board (IRB). Any amendments to the protocol or consent materials must also be approved by the Sponsor and the IRB before they are implemented.

12.2 INFORMED CONSENT

The informed consent form is a means of providing information about the trial to a prospective participant and allows for an informed decision about participation in the study. All participants (or their legally acceptable representative) must read, sign, and date a consent form before participating in the study and undergoing any study-specific procedures. If a participant does not speak and read English, the consent materials must be translated into the appropriate language.

The informed consent form must be updated or revised whenever important new safety information is available, whenever the protocol is amended, and/or whenever any new information becomes available that may affect participation in the trial.

A copy of the informed consent will be given to a prospective participant for review. The study investigator or a qualified study coordinator on the investigator's delegation of responsibility log will review the consent and answer questions. This may be done either in person or remotely. The participant will be informed that participation is voluntary and that he/she may withdraw from the study at any time, for any reason.

Requirements for the assent and informed consent process will depend on the participant's age. Sites will follow their institutional IRB policies to determine the appropriate assent and informed consent process for pediatric participants.

12.3 PRIVACY AND CONFIDENTIALITY

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique sequential identification number by the SACCC. This number, rather than the participant's name or other patient identifiers, will be used to collect, store, and report participant information.

13. PUBLICATION POLICY

The ITN policy on publication of study results will apply to this study. Authorized participants may find details regarding the policy statement on the ITN internet website at [redacted]

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APPENDIX 1. SCHEDULE OF EVENTS

		Years (+/- 60 Days)				
Study Visit	**Screen**	**1**	**2**	**3**	**4**	**5**
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**
General Assessments – Recipient						
Informed Consent	X					
Medical and demographic history including transplant specifics	X					
Contact information for local physician[1]	X					
Inclusion/exclusion criteria[2]	X					
HLA and blood typing (if available)[3]	X					
Concomitant Medications	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X
Clinical outcomes of interest review	X	X	X	X	X	X
Review of all biopsies since last visit, if applicable		X	X	X	X	X
Review of all rejection episodes since last visit, if applicable		X	X	X	X	X
Verify participant has ongoing local follow-up care for transplant		X	X	X	X	X
General Assessments - Donor[3]						
Donor type	X					
Demographics	X					
HLA and blood typing (if available)	X					
Laboratory Assessments						
Hematology - CBC with differential and platelets[4]	X	X	X	X	X	X
Comprehensive Metabolic Panel[5,6]	X[7]	X	X	X	X	X
Fasting Lipid Panel	X	X	X	X	X	X
Urine albumin/creatinine ratio	X	X	X	X	X	X
Urinalysis[8]	X	X	X	X	X	X
Mechanistic Assessments						
Frozen PBMC – flow cytometry panel staining	X	X	X	X	X	X
Frozen PBMC – cellular assays	X	X	X	X	X	X
Serum – HLA alloantibodies, includes DSA, flow PRA	X	X	X	X	X	X
Whole blood – RNA gene expression profiling	X	X	X	X	X	X
Urine pellet – gene expression profiling	X	X	X	X	X	X
Fecal - microbiome profiling	X	X	X	X	X	X

[1] For local clinical care provider who is providing active follow-up care for the participant's single organ liver or kidney allograft.
[2] Participants who complete their screening visit remotely must meet all eligibility criteria, with the exception of confirmed normal allograft function, prior to scheduling a sample collection visit.
[3] This is a retrospective collection of data from medical records, or a previous ITN trial if applicable.
[4] If not completed on the same date as the visit's mechanistic assessment, this assessment must be repeated at the time of the visit's mechanistic collection.
[5] Includes Na, K, Cl, HCO3, BUN, creatinine, calcium, glucose, albumin, total bilirubin, direct bilirubin, GGT, AST, ALT, and alkaline phosphatase.
[6] If there is a 25% increase in the value(s) collected during the scheduled annual visit compared to the participant's baseline value, collect all liver function tests (for liver transplant recipients) or all serum creatinine levels (for kidney transplant recipients) since the last visit.
[7] Participants with abnormal allograft function tests will have their allograft function retested for confirmation (see section 6.3). Abnormal test results thought to be affected by confounding factors should be repeated once the confounding condition has resolved. If a repeat assessment is needed to confirm eligibility, the repeat value will be considered the participant's baseline value (see section 3.1.2).
[8] Includes protein, glucose, WBC, and hematuria.
[9] Not indicated for remote visits.

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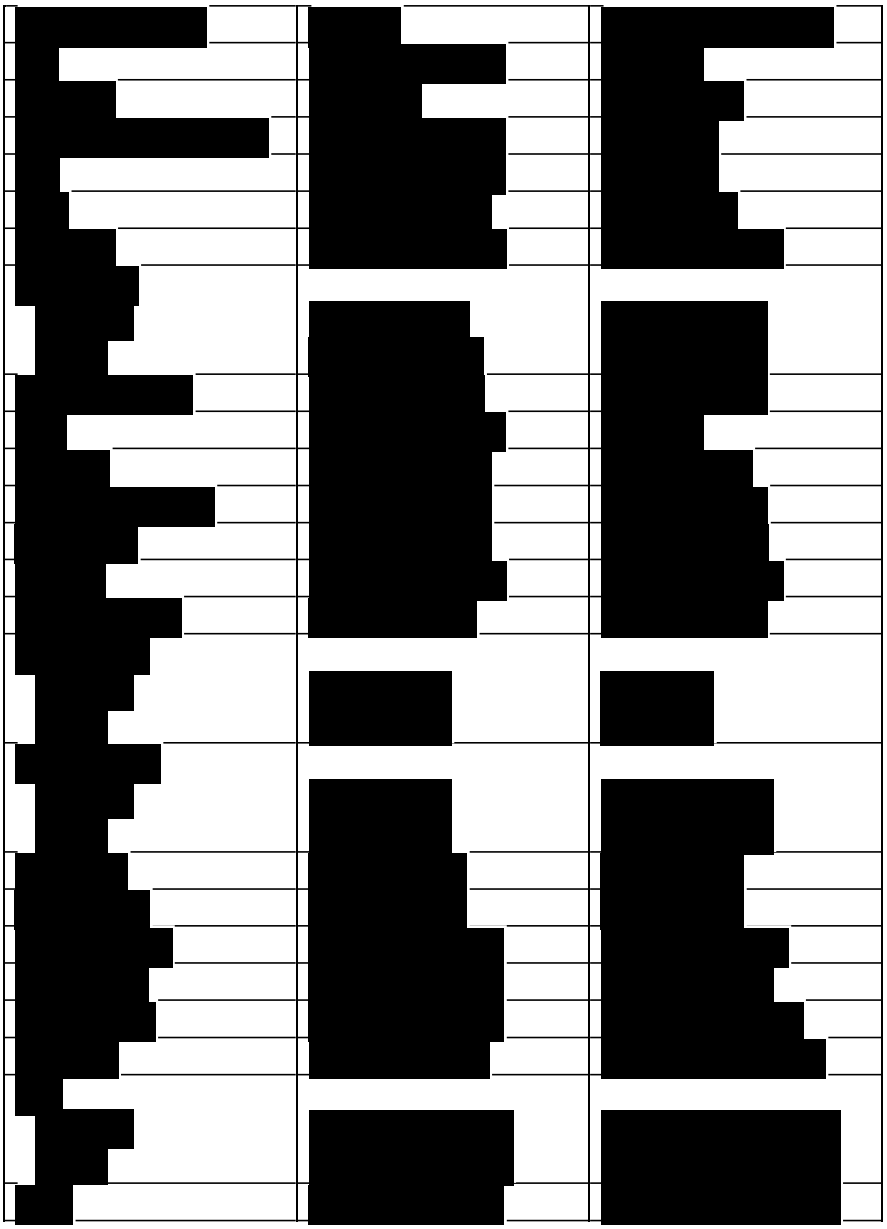

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