Optimizing Immunosuppression Drug Dosing via Phenotypic Precision Medicine

NCT03527238

University of Florida IRB-01 Protocol

TITLE:
Optimizing Immunosuppression Drug Dosing via Phenotypic Precision Medicine

INVESTIGATORS AND STUDY STAFF:
Ali Zarrinpar, Kenneth Andreoni, Mark Johnson, Stephanie Socias, Viki Kim, Shengyi Fu, Danielle Mckimmy (Dean Ho and Chih-Ming Ho at UCLA)

ABSTRACT:
The investigators have developed a computational platform to rapidly identify optimal drug and dose combinations from the innumerable possibilities. By testing this technique termed Phenotypic Personalized Medicine (PPM) in a diverse number of experimental systems representing different diseases, they have found that the response of biological systems to drugs can be described by a low order, smooth multidimensional surface. The main consequence of this is that optimal drug combinations can be found in a small number of tests. This input-output relationship is always based on experimental data, not modeling, and it would lead to a straightforward solution for handling human diversity in drug dosing needs, among other clinical problems. The investigators will test the hypothesis that PPM can be developed and validated for clinical use by conducting a prospective clinical trial to compare the feasibility and efficacy of this approach to standard of care provider dosing. This group has previously used PPM-based optimization to find novel drug combinations in in vitro and in vivo models of cancer and infection. In a published first-in-human study, they compared 4 PPM-dosed patients and 4 control (standard of care dosed) patients. They calculated the tacrolimus dosing regimen using the PPM process and showed significant improvement in variability and a trend toward improved efficacy in achieving goal drug blood-levels. For this application, they aim to show in a larger clinical trial, that PPM is more effective than unaided (standard of care) dosing. This will allow the generation of data to justify a multi-center confirmatory study and to explore a wider array of clinical outcomes to optimize.

BACKGROUND:
The introduction of calcineurin inhibitors like tacrolimus has greatly reduced the incidence of acute rejection and has improved graft and patient survival after transplantation. However, these drugs have narrow therapeutic ranges and serious side-effects. Inter- and intra-individual variability in dosing requirements, particularly across different patient populations, necessitates empirical physician-titrated drug administration that frequently results in deviation from target ranges, particularly during the critical post-operative phase. Multiple studies have shown that high drug level variability is associated with poor long-term outcomes, including rejection and graft loss. As such, there is a clear need for personalized medicine to address post-transplant immunosuppression. However, a robust procedure to achieve personalized coadministration of tacrolimus and other post-transplant drugs has thus far not been available.
Post-transplant immunosuppression provides a challenging model to test any precision medicine platform. Previous studies have sought to personalize tacrolimus dosing using genetics, population pharmacokinetics, and other predictive modeling approaches. However, it is difficult to simultaneously account for the substantial degree of inter- and intra-individual variability in treatment regimens. These differences also lead to health disparities that are not solely attributable to access, socioeconomics, or adherence. Tacrolimus, one of the most widely used immunosuppressants and a mainstay of solid organ transplantation, has a narrow therapeutic index and wide pharmacokinetic variability; it is a substrate of cytochrome P450 and P-glycoprotein (also known as MDR1 or ABCB1), both with genetically variable expression levels in

the intestine and liver. Clearance of tacrolimus is dependent on liver and kidney function, both of which can vary tremendously in the post-transplant setting. Furthermore, all post-transplant patients are on multiple interacting medications. A simple pharmacogenetic algorithm will not be able to respond adequately to the variability.

We have developed a powerful platform that utilizes patient clinical data to construct a Parabolic Response Surface (PRS). The PRS is patient-specific and based on individualized values that represent each patient's response to drug treatment. Examples of this response can be tacrolimus blood trough levels or quantitative markers of organ function or injury. PRS reconciles clinical data into a visual map that enables the immediate identification of optimal drug doses needed to bring drug levels to within the desired range. Importantly, because the PRS process does not require a priori knowledge of disease mechanism, it can efficiently prescribe precise and optimized drug doses despite the frequent changes to patient treatment regimens following transplantation that can have a profound effect on drug metabolism.

SPECIFIC AIMS:

Overall Aim: Prospective randomized clinical trial applying PPM to tacrolimus dosing in liver and/or kidney transplant recipients to show improvement in maintaining drug trough levels within the target range.

Sub-Aim 1: Prospective clinical trial comparing PPM-based dosing with standard of care physician guided dosing in liver and/or kidney transplant recipients to show improvement in time-within-target-range of drug trough levels.

Measures of drug level management will include i) fraction of days outside of target range, ii) fraction of days with large deviations (>2 ng/mL), and iii) ratio of area-under-the-curve outside of target range to total. Clinical measures in both arms will also be monitored to ensure subject safety and correlate trough level maintenance to clinical outcomes.

Sub-Aim 2: Substudy comparing the pharmacokinetics of patients with high variance in tacrolimus dosing with those with low variance.

To examine contributors to variance in tacrolimus dosing, we will measure the pharmacokinetics of a subset of patients in this study and correlate the findings with donor/recipient genetics, changes in drug regimens, and clinical factors such as liver and kidney function. We will use the pharmacokinetic data to interpret the performance of PPM and provide additional validation for our trial.

RESEARCH PLAN:

The aim of this project is to use PPM to uncover valuable and previously unknown information pertaining to patient dose requirements and correlate them with patient clinical and other contextual information. Importantly, because PPM is able to determine patient-specific levels of drug synergism and antagonism, this project is also expected to reveal vital patient subpopulation information in terms of how the modulation of multiple medications may impact tacrolimus levels and/or precision-based measures of immunosuppression at a patient-specific level. In addition, any future discovery of quantitative biomarkers as measures of immunosuppression will serve as a gateway towards even more effective personalized and relevant drug dosing.

Aim: Prospective randomized clinical trial applying PPM to tacrolimus dosing in liver and/or kidney transplant recipients to show improvement in maintaining drug trough levels within the target range.

Sub-Aim 1: Prospective clinical trial applying PPM to tacrolimus dosing in liver and/or kidney transplant recipients to show improvement in management of drug trough levels. This sub-aim constitutes the crux of the proposal. Its key objectives are: 1) to ensure the safety of the subjects; 2) to test the performance of PPM in guiding tacrolimus dosing in order to keep patient drug levels

within target range more frequently, lead to fewer days out of range, and result in smaller deviations from the target range than the standard of care.

Adult patients who have undergone deceased donor liver and/or kidney transplantation will be recruited and randomized 1:1 to standard of care physician-guided dosing or PPM-guided dosing. Patients with contraindications to tacrolimus will be excluded. Following transplantation, patients will be started on a standard of care medication regimen including tacrolimus. For the first 72 hours tacrolimus will be dosed per standard of care. This allows enough data points to be gathered to allow PPM prediction. Blood tacrolimus trough levels will be taken daily. For standard of care subjects, a senior clinical pharmacist will determine the subsequent doses in consultation with the attending surgeon on call. For PPM subjects, de-identified data consisting of the daily treatment regimen details including drugs already administered, drugs to be administered, and hemodialysis or any other procedures to be performed will be sent to the PPM team at UCLA. Following analysis, the PPM team will suggest a tacrolimus dose for clinician (attending surgeon on call) approval prior to administration. In the rare instance that the UCLA team cannot arrive at a recommendation, then the subject will receive the standard of care (physician-guided) tacrolimus dose. Patients will remain on the trial until discharge from the hospital at which point they will all revert to standard of care dosing. Outcome measures will include i) fraction of days outside of target range, ii) fraction of days with large (> 2 ng/mL) deviations, and iii) ratio of area-under-the-curve outside of target range to total. Clinical safety and efficacy measures will also be monitored to ensure subject safety and to correlate trough level maintenance to clinical outcomes. These include adverse events such as neurotoxicity [documented seizures, clinically significant tremors, or imaging-confirmed posterior reversible encephalopathy syndrome (PRES)], nephrotoxicity (biopsy proven acute kidney injury or calcineurin toxicity, anuria or oliguria requiring dialysis), biopsy-proven rejection, need for repeat steroid pulse, graft loss, or death.

Statistical Analysis. Comparative analysis of the effectiveness of PPM dosing will be assessed using area-under-the-curve and variance analysis as in sub-aim 1 above. Based on our preliminary results thirty patients per group will provide greater than 90% power (alpha = 0.05) to show a difference in a two-tail test.

Feasibility, Anticipated Challenges and Proposed Solutions. The UF transplant program performs more than 150 adult liver and/or kidney transplant operations per year. This allows us to complete recruitment in less than 6 months. We do not anticipate major challenges; Dr. Zarrinpar has substantial experience working on the clinical validation of PPM. We have already successfully performed a prospective pilot study with the same protocol. Because of this we have an established protocol that is conducive to markedly improving the treatment outcomes of patients that participate in the study.

Sub-Aim 2: Comparing the pharmacokinetics of patients with high variance in tacrolimus dosing with those with low variance.

Studies in kidney transplant recipients have indicated that cytochrome P450 CYP3A5 genotype and hematocrit account for more than 60% of variability in tacrolimus pharmacokinetics. Data in liver transplant patients is less well characterized but the unexplained variability is likely higher. To examine contributors to variance in tacrolimus dosing, we will measure tacrolimus pharmacokinetics in this study and correlate the findings with donor/recipient genetics, changes in drug regimens, and clinical factors such as liver and kidney function. For each subject, at least three blood samples (pre-dose and 2 and 6 hours after the dose) will be collected on study days 2, 7, and 14. We will use these pharmacokinetic data to interpret the performance of PPM predictions and provide additional validation for our trial. Genotyping of each donor and recipient

will be performed for CYP3A5 and P-glycoprotein to look for their contribution to variance in pharmacokinetics. Both one- and two-compartment models will be evaluated.

Statistical analysis. Similar to the previous sub-aim, comparisons between the two groups will performed using either the two-tailed Welch's t-test or Student's t-test. For nonparametric (non-normal) distributions, a two-tailed Levene's test will be used to compare variances, and a two-tailed Wilcoxon Rank Sum test will be used to compare medians. The number of subjects in this study is similar to that in the study by Gerard et al in their approach to building a model for determination of tacrolimus trough blood concentrations.

Data Safety Monitoring Plan. The Principal Investigator (PI) will be responsible for ensuring participants' safety on a daily basis. Given the low risk status of this study with minimal impact on patient care, a Data and Safety Monitoring Board will not be required. Furthermore, each liver/kidney transplant patient is closely followed by a large group consisting of the clinical transplant team (surgeons, hepatologists, pharmacist, nurse coordinators) and the transplant administrative team (transplant program managers and quality officers). One-month, one-year, and three-year outcomes are monitored closely and reporting on patient quality is mandated by the United Network for Organ Sharing (UNOS). Dedicated statisticians in the transplant program monitor real-time outcomes and report them in weekly emails and monthly quality meetings.
A Data Safety Monitoring Board will additionally be appointed. It will include a transplant hepatologist, a transplant nephrologist, and a biostatistician not involved in the study. We will perform an interim analysis comparing the occurrence of i) biopsy-proven rejection episodes, and ii) fraction of days with large (> 2 ng/mL) deviations after ten patients have been randomized into each arm (twenty total subjects). The board will meet after enrollment of 10 patients into each arm (to evaluate the interim analysis) and then every six months thereafter until study completion. The study will be stopped in the event there is a significant unacceptable difference between the two groups. The biostatistical consulting service at the CTSI will assist in monitoring study enrollment, safety signals, and achievement of targets.

Protection of patient medical records: To ensure that patient information is de-identified/anonymized, we will abstract all data (images, lab, clinical data etc.) onto a page or file with only the anonymization codes with no personal identifiers or utilize protocols/programs that will be able to redact the personal identifiers when uploading them as data for study. The code key will only be available to the Project PI and authorized personnel and kept in a secure, locked location. Upon completion of the study, this coded template/anonymization key will be discarded according to regulations. The PI will oversee this task.

POSSIBLE DISCOMFORTS AND RISKS:
Risks of PPM-guided dosing of therapeutic agents to optimize patient-specific immunosuppression include:

- The administration of a drug dose that varies from those given based on clinical practice. This may result in over-dosing or under-dosing. The risks of chronic over-dosing include altered mental status and renal injury. The risks of chronic under-dosing include possible rejection. Both of these risks are mitigated by the fact that blood drug levels are tested daily and deviations will be corrected.
- For Sub-Aim 2, additional blood draws will need to be performed (2 and 6 hours after the dose), on postoperative days 2, 7, and 14. (The pre-dose blood draw is standard of care.)

- Patient medical records will need to be accessed during the study. Therefore, there is a risk of exposure of PHI. Patient-record access and subsequent anonymizing and de-identification of records will be implemented (as indicated above).

Protection Against Risks: The PPM process is not automated. PPM-suggested doses are always based on implicit limits set by the clinical team so that doses will always be within clinically-relevant levels. Most importantly, the administered dose will always be selected by the supervising physician following consultation with the PPM team.

The blood draws will be performed by trained phlebotomists and will not exceed 7 mL per blood draw for a total of 42 mL over two weeks at maximum.

POSSIBLE BENEFITS:
The subjects themselves may or may not benefit from being part of this study. The PPM process has the potential to optimize tacrolimus dosing for the patients on the treatment arm. For the population at large, the ability to definitively optimize dosing will enable the accurate correlation of genomic factors with dosing trends. This may ultimately help eliminate health disparities in not only transplantation but other indications as PPM is broadly applicable and scalable.

Importance of Knowledge to Be Gained: While it is well known that dosing trends vary between subpopulations based on demographic or pharmacogenomic profiles, it has been challenging to definitively construct accurate and robust subpopulation-specific regimens due to the previous inability to correlate genomic or ethnic information with dose response. The application of PPM that will result in individualized and optimized regimens to be developed for each patient in this study will allow the investigators to correlate information in a way that was previously not possible. This will open new doors to improving treatment outcomes in the form of graft/patient survival for transplant immunosuppression, or other indications in oncology, infectious diseases, and other applications.

CONFLICT OF INTEREST:
None.

UF | Institutional Review Board
UNIVERSITY of FLORIDA

INFORMED CONSENT FORM
to Participate in Research, and

AUTHORIZATION
to Collect, Use, and Disclose Protected Health Information (PHI)

INTRODUCTION

Name of person seeking your consent:_____

Place of employment & position: _____

Please read this form which describes the study in some detail. A member of the research team will describe this study to you and answer all of your questions. Your participation is entirely voluntary. If you choose to participate you can change your mind at any time and withdraw from the study. You will not be penalized in any way or lose any benefits to which you would otherwise be entitled if you choose not to participate in this study or to withdraw. If you have questions about your rights as a research subject, please call the University of Florida Institutional Review Board (IRB) office at (352) 273-9600.

GENERAL INFORMATION ABOUT THIS STUDY

1. Name of Participant ("Study Subject")

_____

2. What is the Title of this research study?

Optimizing Immunosuppression Drug Dosing via Phenotypic Precision Medicine

3. Who do you call if you have questions about this research study?

Principal Investigator: Ali Zarrinpar, MD, PhD – 352-265-0606

After Hours: 352-265-0535

4. Who is paying for this research study?

The sponsor of this study is the National Institutes of Health

5. In general, what do you need to know about this Research Study?

Agreeing to become involved in any research is always voluntary. By signing this form, you are not waiving any of your legal rights. If you decide not to participate in this research, you will not be penalized in any way and you will not lose any benefits to which you are entitled. If you have questions about your rights as a research subject, please call the University of Florida Institutional Review Board (IRB) office at (352) 273-9600.

a) In general, what is the purpose of the research, how long will you be involved?

The purpose of this research study is to see if there are computer based methods that can improve the dosing of your immunosuppression drug tacrolimus.

You are being asked to be in this research study because you received a liver and/or kidney transplant.

You will be involved in this study for as long as you remain in the hospital after your transplant.

b) What is involved with your participation, and what are the procedures to be followed in the research?

Information from your medical record about your operation such as your age, race, ethnicity, and sex, and test results about your operation will be used. This information will be sent to the computation team at UCLA for analysis. We will also do the following:

You will be assigned to either the group that gets regular care (unassisted dosing) or the group whose drug dosing will be assisted by a computer based calculation. The assignment will be random (much like a flip of a coin) and equal between the two groups. You will not know which group you are assigned to. The computer based calculation will start making recommendations three days after your transplant.

We may collect extra blood draws on you. 2, 7, and 14 days after the transplant (if you are still in the hospital), we may draw about 1 teaspoon of blood 2 and 6 hours after you take your dose of tacrolimus in the morning to determine your tacrolimus level.

We may also be performing a limited genetic test on you and your donor to see if differences in two genes (CYP3A5 and P-glycoprotein) can explain the variability in your dosing.

c) What are the likely risks or discomforts to you?

It is possible that the new computer method might recommend doses that are either too high and more likely to be associated with altered mental status or kidney injury, or too low and more likely to be associated with rejection. However, the risk of it happening is very low because ultimately, the study doctors will make the final decision as to whether or not the computer's recommendations is the best course.

Also, blood draws may be performed (2 and 6 hours after the dose), on postoperative days 2, 7, and 14. (The pre-dose blood draw is standard of care.) Complications of blood drawing may include pain, infection at site, bruising, swelling at the site, and rarely fainting. You will have a medically necessary catheter in place already for your care, so no new needle sticks will be required.

Researchers will take appropriate steps to protect any information they collect about you. However, there is a slight risk that information about you could be revealed accidentally.

d) What are the likely benefits to you or to others from the research?

It is possible that computer assisted dosing could help you reach the ideal immunosuppression doses faster than the standard-of-care approach. This would minimize your hospital stays, clinic visits and lab draws. It could also minimize risks for drug toxicities and/or rejection.

Developing computer assisted dosing that provides more effective immunosuppression drug dosages can reduce the number of transplant rejections and less clinic visits you or the others would need post operatively. This may lead to fewer changes in drug levels and may lead to having lower risks/complications from transplant rejection or kidney injury.

e) What are the appropriate alternative procedures or courses of treatment, if any, that might be helpful to you?

Other than the standard-of-care provided to you before, during and after the transplant surgery, there are no other alternative procedures to the computer assisted dosing used in this study that might be helpful to you.

Additional and more detailed information is provided within the remainder of this Informed Consent form, please read before deciding if you wish to participate in this study

WHAT CAN YOU EXPECT IF YOU PARTICIPATE IN THIS STUDY?

6. What will be done as part of your normal clinical care (even if you did not participate in this research study)?

You have had your operation. You normal after transplant clinical care will be decided by your doctors.

7. What will be done only because you are in this research study?

Information from your medical record about your operation such as your age, race, ethnicity, and sex, and test results about your operation will be used. This information will be sent to the computation team at UCLA for analysis. We will also do the following:

You will be assigned to either the group that gets regular care (unassisted dosing) or the group whose drug dosing will be assisted by a computer based calculation. The assignment will be random (much like a flip of a coin) and equal between the two groups. You will not know which group you are assigned to. The computer based calculation will start making recommendations three days after your transplant.

We may also be doing extra blood draws on you. 2, 7, and 14 days after the transplant (if you are still in the hospital), we may draw about 1 teaspoon of blood 2 and 6 hours after you take your dose of tacrolimus in the morning to determine your tacrolimus level.

We may also be performing a limited genetic test on you and your donor to see if differences in two genes (CYP3A5 and P-glycoprotein) can explain the variability in your dosing.

Once this research study is completed, any information that could identify you **might** be removed from any identifiable private information or identifiable biospecimens collected and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or your legally authorized representative

If you have any questions now or at any time during the study, please contact one of the research team members listed in question 3 of this form.

8. How long will you be in this research study?

You will be in this study for as long as you remain in the hospital after your transplant.

9. How many people are expected to take part in this research study?

Sixty adult patients who have undergone deceased donor liver and/or kidney transplantation will be recruited and assigned to either standard of care physician-guided dosing or PPM-guided dosing.

WHAT ARE THE RISKS AND BENEFITS OF THIS STUDY AND WHAT ARE YOUR OPTIONS?

10. What are the possible discomforts and risks from taking part in this research study?

It is possible that the new computer method might recommend doses that are either too high and more likely to be associated with altered mental status or kidney injury or too low and more likely to be associated with rejection. We believe that the risk of this is low because the computer method is being used as a guide and the study doctors will make the final decision as to whether or not to follow the computer's recommendations.

Also additional blood draws will need to be performed (2 and 6 hours after the dose), on postoperative days 2, 7, and 14. (The pre-dose blood draw is standard of care.) The complications of blood drawing may include pain, infection at site, bruising, swelling at the site, and rarely fainting. You will have a medically necessary catheter in place already for your care, so no new needle sticks will be required.

Researchers will take appropriate steps to protect any information they collect about you. However, there is a slight risk that information about you could be revealed inappropriately or accidentally. Depending on the nature of the information, such a release could upset or embarrass you, or possibly affect your insurability or employability. Questions 17-21 in this form discuss what information about you will be collected, used, protected, and shared.

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. Additional information can be obtained at: http://irb.ufl.edu/gina.html or call 1-800-669-3362. If you think this law has been violated, it will be up to you to pursue any compensation from the offending insurance company and/or employer.

This study may include risks that are unknown at this time.

Participation in more than one research study or project may further increase the risks to you. If you are already enrolled in another research study, please inform one of the research team members listed in question 3 of this form or the person reviewing this consent with you before enrolling in this or any other research study or project.

Throughout the study, the researchers will notify you of new information that may become available and might affect your decision to remain in the study.

If you wish to discuss the information above or any discomforts you may experience, please ask questions now or call one of the research team members listed in question 3 in this form.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You have been informed that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information. That is, if you give written consent for the release of information, we cannot withhold that information and we cannot hold responsibility for how that person may use your information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under the following circumstances. If we learn about child abuse, elder abuse, or intent to harm yourself or others, we will report that information to appropriate authorities.

11a. What are the potential benefits to you for taking part in this research study?

It is possible that computer assisted dosing will improve how fast your immunosuppression doses will be arrived at. This would minimize your hospital stays, clinic visits, and lab draws. It could also minimize risks for drug toxicities and/or rejection.

11b. How could others possibly benefit from this study?

The creation of computer assisted dosing that provides more effective and consistent immunosupression drug dosages can potentially reduce the number of transplant rejections that occur and reduction of clinic visits patients would be required post operatively. This may lead to less changes in drug levels and may improve outcomes such as lower risks/complications from transplant rejection or kidney injury.

11c. How could the researchers benefit from this study?

In general, presenting research results helps the career of a scientist. Therefore, the Principal Investigator listed in question 3 of this form may benefit if the results of this study are presented at scientific meetings or in scientific journals.

12. What other choices do you have if you do not want to be in this study?

As this is not a treatment study, the alternative to participating in the study is not to participate in the study and just get regular standard of care.

13a. Can you withdraw from this study?

You are free to withdraw your consent and to stop participating in this study at any time. If you do withdraw your consent, you will not be penalized in any way and you will not lose any benefits to which you are entitled. If you decide to withdraw your consent to participate in this study for any reason, please contact one of the research team members listed in question 3 of this form. They will tell you how to stop your participation safely.

If you have any questions regarding your rights as a research subject, please call the Institutional Review Board (IRB) office at (352) 273-9600.

13b. If you withdraw, can information about you still be used and/or collected?

Because this study is federally funded, basic information about your participation will be kept. Otherwise, any identifiable information about you will be safely discarded.

13c. Can the Principal Investigator withdraw you from this study?

You may be withdrawn from the study without your consent for the following reasons:

- if your safety and welfare are at risk or if you do not follow instructions.

WHAT ARE THE FINANCIAL ISSUES IF YOU PARTICIPATE?

14. If you choose to take part in this research study, will it cost you anything?

There is no cost to you for participating in this research study.

15. Will you be paid for taking part in this study?

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

16. What if you are injured because of the study?

If you are injured as a direct result of your participation in this study, only the professional services that you receive from any University of Florida Health Science Center healthcare provider will be provided without charge. These healthcare providers include physicians, physician assistants, nurse practitioners, dentists or psychologists. Any other expenses, including Shands hospital expenses, will be billed to you or your insurance provider.

You will be responsible for any deductible, co-insurance, or co-payments. Some insurance companies may not cover costs associated with research studies or research-related injuries. Please contact your insurance company for additional information.

The Principal Investigator will determine whether your injury is related to your participation in this study.

No additional compensation is routinely offered. The Principal Investigator and others involved in this study may be University of Florida employees. As employees of the University, they are protected under state law, which limits financial recovery for negligence.

Please contact one of the research team members listed in question 3 of this form if you experience an injury or have questions about any discomforts that you experience while participating in this study.

17. How will your health information be collected, used and shared?

If you agree to participate in this study, the Principal Investigator will create, collect, and use private information about you and your health. This information is called protected health information or PHI. In order to do this, the Principal Investigator needs your authorization. The following section describes what PHI will be collected, used and shared, how it will be collected, used, and shared, who will collect, use or share it, who will have access to it, how it will be secured, and what your rights are to revoke this authorization.

Your protected health information may be collected, used, and shared with others to determine if you can participate in the study, and then as part of your participation in the study. This information can be gathered from you or your past, current or future health records, from procedures such as physical examinations, x-rays, blood or urine tests or from other procedures or tests. This information will be created by receiving study treatments or participating in study procedures, or from your study visits and telephone calls. More specifically, the following information may be collected, used, and shared with others:

- The research team, authorized UF personnel, and regulatory agencies such as the Food and Drug Administration (FDA), may have access to study data and records to monitor the study. Research records provided to authorized, non-UF personnel will not contain identifiable information about you. Publications and/or presentations that result from this study will not identify you by name.

This information will be stored in locked filing cabinets or on computer servers with secure passwords, or encrypted electronic storage devices.

Some of the information collected will be included in a "limited data set" to be used for other research purposes, including sending to the computation team at UCLA for analysis and dose recommendations. The limited data set will only include information that does not directly identify you. For example, the limited data set will not include your name, address, telephone number, social security number, photographs, or other codes that link you to the information in the limited data set. Agreements between the parties creating and receiving the limited data set have been established in order to protect your identity and confidentiality and privacy.

18. For what study-related purposes will your protected health information be collected, used, and shared with others?

Your PHI may be collected, used, and shared with others to make sure you can participate in the research, through your participation in the research, and to evaluate the results of the research study. More specifically, your PHI may be collected, used, and shared with others for the following study-related purpose(s):

- The purpose of this research study is to see if there are computer based methods that can improve the dosing of your immunosuppression drug tacrolimus after your liver and/or kidney transplant.

- The research team, authorized UF personnel, and regulatory agencies such as the Food and Drug Administration (FDA), may have access to study data and records to monitor the study. Research records provided to authorized, non-UF personnel will not contain identifiable information about you. Publications and/or presentations that result from this study will not identify you by name.

Once this information is collected, it becomes part of the research record for this study.

19. Who will be allowed to collect, use, and share your protected health information?

Only certain people have the legal right to collect, use and share your research records, and they will protect the privacy and security of these records to the extent the law allows. These people include:

- the study Principal Investigator (listed in question 3 of this form) and research staff associated with this project.
- other professionals at the University of Florida or Shands Hospital that provide study-related treatment or procedures.
- the University of Florida Institutional Review Board (IRB; an IRB is a group of people who are responsible for looking after the rights and welfare of people taking part in research).

20. Once collected or used, who may your protected health information be shared with?

Your PHI may be shared with:

- the study sponsor (listed in Question 4 of this form).
- United States governmental agencies who are responsible for overseeing research, such as the Food and Drug Administration, the Department of Health and Human Services, and the Office of Human Research Protections .
- Government agencies who are responsible for overseeing public health concerns such as the Centers for Disease Control and federal, state and local health departments.

Otherwise, your research records will not be released without your permission unless required by law or a court order. It is possible that once this information is shared with authorized persons, it could be shared by the persons or agencies who receive it and it would no longer be protected by the federal medical privacy law.

21. If you agree to take part in this research study, how long will your protected health information be used and shared with others?

Your PHI will be used and shared with others until the end of the study.

You are not required to sign this consent and authorization or allow researchers to collect, use and share your PHI. Your refusal to sign will not affect your treatment, payment, enrollment, or eligibility for any benefits outside this research study. However, you cannot participate in this research unless you allow the collection, use and sharing of your protected health information by signing this consent and authorization.

You have the right to review and copy your protected health information. However, we can make this available only after the study is finished.

You can revoke your authorization at any time before, during, or after your participation in this study. If you revoke it, no new information will be collected about

you. However, information that was already collected may still be used and shared with others if the researchers have relied on it to complete the research. You can revoke your authorization by giving a written request with your signature on it to the Principal Investigator.

SIGNATURES

As an investigator or the investigator's representative, I have explained to the participant the purpose, the procedures, the possible benefits, and the risks of this research study; the alternative to being in the study; and how the participant's protected health information will be collected, used, and shared with others:

Signature of Person Obtaining Consent and Authorization	Date

You have been informed about this study's purpose, procedures, possible benefits, and risks; the alternatives to being in the study; and how your protected health information will be collected, used and shared with others. You have received a copy of this Form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask questions at any time.

You voluntarily agree to participate in this study. You hereby authorize the collection, use and sharing of your protected health information as described in sections 17-21 above. By signing this form, you are not waiving any of your legal rights.

Signature of Person Consenting and Authorizing	Date