Title of Research Study: *Comparison of the cognitive and motor effects of treatment between an immediate- and extended-release tacrolimus (Envarsus® XR) based immunosuppression regimen in kidney transplant recipients*

Researcher Team Contact Information: For questions about research appointments, the research study, research results, or other concerns, call the study team at:

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Financial Interest Disclosure: The following disclosure is made to give you an opportunity to decide if this relationship will affect your willingness to participate in this research study:

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

What is research?

Doctors and researchers are committed to your care and safety. There are important differences between research and treatment plans:

- The goal of research is to learn new things in order to help groups of people in the future. Researchers learn things by following the same plan with a number of participants, so they do not usually make changes to the plan for individual research participants. You, as an individual, may or may not be helped by volunteering for a research study.
- The goal of treatment is to help you get better or to improve your quality of life. Doctors can make changes to your treatment plan as needed.

What should I know about a research study?

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

Why am I being asked to take part in this research study?

You are being asked to take part in this research study because you are between 18 and 65 years of age and have had a kidney transplant after which you were placed on the anti-rejection (known as an "immunosuppressant") medication, tacrolimus.

Why is this research being done?

The purpose of this study is to find out if there is a difference between how two different formulations of tacrolimus, one that is taken twice a day (immediate release) and the other that is taken once a day (extended release), affect your thinking, motor function, and how well you feel in general.

Though tacrolimus is one of the most frequently used medications to prevent the body from rejecting the transplanted kidney, like similar anti-rejection drugs that suppress the immune system, it may cause unwanted side effects such as memory problems, confusion, and tremor in approximately 10-28% of patients.

How long will the research last?

We expect that you will be in this research study for approximately eight (8) months.

Number of Participants

This study is only being conducted at the University of Minnesota. We expect about 74 people to participate.

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

If you agree to participate in this study, we would ask you to complete the following tasks listed below. All of the visits will occur at University of Minnesota Health Clinics and Surgery Center, 909 Fulton St SE, Minneapolis, MN 55455.

If you do choose to sign consent, your doctor or another authorized member of the research team will also sign this consent, confirm you are suitable to take part in this study and collect the following information:

- Demographics – information such as your age, gender and ethnicity.
- The medical history related to your renal disease.
- Any treatments for your renal disease
- We would then ask you to do the following: After you receive your transplant and, as part of your standard care, are placed on the immunosuppressant tacrolimus, cognitive and motor function testing will be administered by the study coordinator on five (5) separate occasions (i.e., visits). Each visit, which may coincide with your regularly scheduled clinic visit, should not last longer than one (1) hour. The testing will occur as follows:

Visit 1 (Pre-Baseline) can occur no sooner than two (2) to three (3) months after your transplant and after being placed on immediate-release tacrolimus. The purpose of this visit is to familiarize you with the instructions and nature of the cognitive and motor function tests that you will be taking four (4) more times over the course of the study. Visit 1 should last less than one (1) hour, after which the study coordinator will schedule you for Visit 2 (Baseline).

Visit 2 (Baseline) will occur no more than 60 days prior to Visit 1. One (1) 10-ml (approx. 2 teaspoons) blood sample will be collected, which is standard care if the visit coincides with a regularly scheduled clinical visit. If you agree, a portion of this blood sample will be used to see if you have variations of specific genes that are known to affect how the drug works in your body. The study coordinator will then administer the cognitive and motor function tests (see "Cognitive and motor testing" below), after which you will be asked to fill out self-report measures of health-related quality of life. The testing session should take approximately 30-45 minutes to complete. After the testing, you will be randomly assigned to either: a) the group that will remain on immediate-release tacrolimus (twice daily) for the duration of the study (**IR group**) or b) be switched by your physician to the extended-release (once daily: Envarsus®XR) formulation of tacrolimus (**XR group**) for the remainder of the study.

Envarsus®XR is an FDA approved form of the anti-rejection drug, tacrolimus, for people who have had a kidney transplant, that is taken once daily. It has been shown to be as effective as immediate-release, twice-daily, tacrolimus and poses no additional risks when dosed and taken as prescribed by your doctor. You will be chosen to switch to Envarsus®XR by chance, like flipping a coin.

Visit 3 will occur approximately six (6) weeks after Visit 2. For both the IR and XR groups, a single blood sample (approx. 2 teaspoons) will be collected. The study coordinator will then administer alternate versions of the same cognitive and motor function tests you were given during Visit 2. You will once again be asked to complete self-report measures of health-related quality of life.

Visit 4 will occur approximately six (6) weeks after Visit 3. The same procedures will be

followed as in Visit 3.

Visit 5 will occur approximately 12 weeks after Visit 4. The same procedures will be followed as in Visit 3.

You will be in this study for approximately eight (8) months.

A total of approximately eight (8) teaspoons of blood will be collected over the entire study.

- *Cognitive and motor function testing*: At each visit, you will be administered a number of tasks that you will be asked to complete. They will be conducted in a private clinic room. Some of these will require you to write, others will be given orally. These tasks are designed to measure various aspects of your thinking and motor function and will take less than one (1) hour to complete. Your responses to these tests will be recorded on an iPAD. Tremor assessment will require video recording.

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

It is expected that you will:

- Take all your medication as prescribed
- Show up at all visits at your scheduled time
- Contact the study coordinator at least 24 hours prior to your scheduled visit if you need to reschedule
- Put forth your best effort on all testing procedures

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

You can decide not to participate in this study or leave the research at any time and it will not be held against you. You will continue receiving standard of care treatment from your physician.

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

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

If you withdraw your consent you will not be able to continue with the study. Your decision to take part or not take part will in no way affect your current or future treatment and your doctor will continue to treat you for your condition. If you decide to withdraw from the study, please contact the study coordinator, your doctor or one of his staff. If your condition changes during the study or you are not taking part in the study as we would expect you to, you may be withdrawn from the study without your consent.

If you withdraw your consent, your study doctor will no longer use or disclose any more of your medical information. However, the information that has already been sent to the sponsor cannot be retrieved or destroyed and may be used as part of the study.

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

You will be informed, in a timely manner, if any information becomes available that may affect your willingness to participate in this study.

What are the risks of being in this study? Is there any way being in this study could be bad for me?

This study does not involve any medical treatment other than the ones prescribed by your doctor, nor does it involve any additional medical procedures. If you are chosen to switch to Envarsus®XR, you will do so under the supervision of your doctor, who will be following FDA on-label dosing and monitoring guidelines. There are no risks to the administration cognitive and motor function tests or self-report measures.

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

There is no harm to a pregnancy or fetus from administering the cognitive and motor testing battery though becoming pregnant or childbirth may influence the outcomes of the study. As part of standard care, a serum or urine pregnancy test is administered within seven (7) days prior to transplant and potential subjects must have a negative result. Moreover, if heterosexually active, you agree to consistently use two forms of highly effective birth control (at least one of which must be a barrier method) which includes consistent and correct usage of established oral contraception, established intrauterine device or intrauterine system, or barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, starting at screening and throughout the study period and for 90 days after the final study drug administration.

If you are considered to be postmenopausal (defined as at least 1 year without any menses), you are not required to use contraception while participating in this research study.

If you become pregnant while participating in this research study or for three (3) months after you complete the study, it is important that you tell the study doctor or other research team member immediately. You may be required to stop participating in this study.

If you are female, you must agree not to breastfeed or to donate ova starting at screening and throughout the study period, and for 90 days after the final study drug administration.

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

There is no cost to you, your private medical insurance (if any), or the public health insurance plan, for study procedures. There will be no additional medical costs to you for taking part in this study outside any usual costs related to any visit to your doctor.

Will being in this study help me in any way?

No one knows if there will be any benefit to you from this study. We cannot promise any benefits to you or others from your taking part in this research. However, we hope that the information we learn from this study can be used in the future to help other kidney transplant recipients who are taking the anti-rejection medication, tacrolimus.

What happens to the information collected for the research?

Efforts will be made to limit the use and disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete secrecy. Organizations that may inspect and copy your information include the IRB and other representatives of this institution. In addition, other individuals such as monitors, auditors and representatives from the sponsor company, or regulatory authorities (such as the US Food and Drug Administration – US FDA) may also need access to your medical information. We will do everything we can to make sure that your medical information is kept confidential.

We will not ask you about child [or elder] abuse, but if you tell us about child [or elder] abuse or neglect, we may be required or permitted by law or policy to report to authorities.

You will be identified by a number on any forms used for this study and your personal information relating to this study will be kept in a secure location by the study team for a minimum of two years after completion of the research study.

You have the right to check your study records and request changes if the information is not correct.

The sponsor, monitors, auditors, the IRB, the University of Minnesota Research Compliance Office and other University compliance units, the US Office of Research Integrity (ORI), the US Office for the Protection of Human Research Protections (OHRP), the US Food and Drug Administration (FDA) may be granted direct access to your medical records to conduct and oversee the research. By signing this document you are authorizing this access. We may publish the results of this research, but your identity will remain confidential. Only aggregated data will be published. A description of this clinical trial will be available at http://www.ClinicalTrials.gov , as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Your consent is required to take part in this study. By signing this information and consent form, you consent to the collection, access, use and disclosure of your information as described above. Your consent does not have an expiration date. You do not have to sign this information and consent form, but if you do not, you will not be able to take part in this research study. You will be able to withdraw your consent at any time, by communicating with your study team; in this

case you will stop taking part in this study.

While every effort will be made to protect the privacy of your information, absolute confidentiality cannot be guaranteed. This does not limit the duty of the researchers and others to protect your privacy.

Will anyone besides the study team be at my consent meeting?
You may be asked by the study team for your permission for an auditor to observe your consent meeting (or a recording of your consent meeting). Observing the consent meeting is one way that the University of Minnesota makes sure that your rights as a research participant are protected. The auditor is there to observe the consent meeting, which will be carried out by the people on the study team. The auditor will not record any personal (e.g., name, date of birth) or confidential information about you. The auditor will not observe your consent meeting (or a recording of your consent meeting) without your permission ahead of time.

Who do I contact if I have questions, concerns or feedback about my experience?

This research has been reviewed and approved by an Institutional Review Board (IRB) within the Human Research Protections Program (HRPP). To share feedback privately with the HRPP about your research experience, call the Research Participants' Advocate Line at 612-625-1650 or go to https://research.umn.edu/units/hrpp/research-participants/questions-concerns. You are encouraged to contact the HRPP if:

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

Will I have a chance to provide feedback after the study is over?
After the study, you might be asked to complete a survey about your experience as a research participant. You do not have to complete the survey if you do not want to. If you do choose to complete the survey, your responses will be anonymous.

If you are not asked to complete a survey after the study is over, but you would like to share feedback, please contact the study team or the Human Research Protection Program (HRPP). See the "Who Can I Talk To?" section of this form for study team and HRPP contact information.

Can I be removed from the research without my OK?
The person in charge of the research study or the sponsor can remove you from the research study without your approval. Possible reasons for removal include failure to show up for study visits; unwillingness to complete the testing battery; pregnancy; determination by treating doctor that there is a reason to significantly alter your drug regimen at any time during the study, including switching to an alternate immunosuppressant.

What else do I need to know?
In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injury will be billed in the ordinary manner to you or your insurance company. If you think that you have suffered a research related injury, let the study physicians know right away.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Will I be compensated for my participation?
If you agree to take part in this research study, we will pay you $50 for each of the five (5) study sessions (a total of $250 if you complete all 5 visits) for your time and effort. You will also be eligible for up to a total of $200 in travel expenses (reimbursed at $0.535 per mile round trip) for Visits 2-5. If you cannot continue or choose to drop out of the study, your payment will be prorated for the sessions completed. Compensation will be issued from the University of Minnesota.

Use of Identifiable Health Information

We are committed to respect your privacy and to keep your personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal health information that includes health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number or social security number. Those persons who get your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission. Please read the HIPAA Authorization form that we have provided and discussed.

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

Optional Elements:
The following research activities are optional, meaning that you do not have to agree to them in order to participate in the research study. Please indicate your willingness to participate in these optional activities by placing your initials next to each activity.

I agree	**I disagree**	
_____	_____	The researcher may audio or video record me for use in scholarly presentations or publications. My identity may be shared as part of this activity, although the researcher will attempt to limit such identification. I understand the risks associated with such identification.
_____	_____	The researcher may contact me in the future to see whether I am interested in participating in other research studies by the Principal Investigator of this study.
_____	_____	The researcher may retain any leftover blood samples taken during the study. These samples may be used for other research not related to this study. These samples will be retained in non-identifiable form, meaning that there will be no information associated with the blood or samples that will allow anyone to readily ascertain my identity.

Signature Block for Capable Adult:

If you choose to participate in the genetics portion of the study we will not store the genetics sample indefinitely; in addition, no testing other than for specific RNA or DNA will be done unless we have contacted you and received permission to do so. Please check your preference below:

_____ YES, it is okay to collect a blood sample for genetics testing, as described above.
_____ NO, do not collect a blood sample for genetics testing, as described above.

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

_____ _____
Signature of Participant Date

_____
Printed Name of Participant

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Person Obtaining Consent