PROTOCOL TITLE:

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

PRINCIPAL INVESTIGATOR or FACULTY ADVISOR:

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N/A

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CLINICAL TRIALS REGISTRATION:

NCT03437577

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	11/07/2017	• If subject consents to genetic portion of study, a portion of the baseline blood sample will be used to see if subject has variations of specific polymorphisms that are known to affect drug metabolism.	Yes - Added to consent form dated 11/07/2017
2	11/17/2017	• Added a +/- 7 day visit window to add to flexibility for subject scheduling. • Updated the name of the research team from TRO to SurgCTO. • Removed the Revised Token Test from the list of assessments to be completed at study visits. • Removed sentence stating subjects may be approached with study specific information pre-transplant. Subjects may still be told pre-transplant that they may be approached for studies post-transplant. • Removed Prograf from the protocol and left the immediate-release as a general term because the subjects may be on a generic formulation instead of a brand name formulation	No
3	05/01/2018	• Subjects may now complete pre-baseline visit up to 12 months post-transplant • Updated study visits to accommodate the expansion of the enrollment window to 12 months post-transplant	Yes – Added to consent form dated 05/01/2018
4	06/04/2018	• Fix wording issue – clarified that BASELINE occurs no more than 60 days AFTER PRE-BASELINE • Removed “standard of care” wording as this has changed	Yes – Added to consent form dated 06/04/2018

		since the previous version	
5	07/31/2018	Added information into section 18.0 of the protocol.	Yes – consent form dated 07/31/2018
6	09/11/2018	• Subjects may now complete pre-baseline visit up to 36 months post-transplant • Updated study visits to accommodate the expansion of the enrollment window to 36 months post-transplant	
7	09/06/2019	• Increase age range to "18 and above" • Eliminate study visit (#5) at 24-weeks post baseline, which lowers total compensation to $200 and shortens total study duration	Yes – consent form dates 09/06/2019

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ABBREVIATIONS/DEFINITIONS

- COWA: Controlled Oral Word Association
- Immediate Release: IR
- Extended Release: XR

STUDY SUMMARY

Study Title	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
Study Design	Between four (4) and 38 months after receiving a kidney transplant and having been placed on an immediate-release (IR) tacrolimus immunosuppressant regimen, participants in this study will undergo cognitive and motor function testing and have a blood sample collected (BASELINE). Half of the participants will then be randomly converted to extended-release (XR) tacrolimus (*Envarsus® XR*) while the other half will remain on IR tacrolimus for the duration of the study. Both the IR and XR groups will repeat the cognitive and motor function testing and have a blood sample collected at 6 and 12 weeks Post-BASELINE. A practice version of the cognitive and motor function tests will be administered no more than 60 days before the baseline visit (Pre-BASELINE). Alternate versions of the cognitive and motor tests will be used at each Post-BASELINE testing session to control for possible practice effects.
Primary Objective	The primary objective is to compare the effect of treatment with an immediate-release tacrolimus to an extended-release tacrolimus (i.e., Envarsus® XR) immunosuppressive regimen on cognitive and motor function in kidney transplant recipients.
Secondary Objective(s)	The secondary objective is to determine the factors that explain inter-individual variability in cognitive response. Pharmacokinetic and demographic factors will be explored. Variability in cognitive response between individuals can be large. A population approach (nonline*ar, mixed effects)* will be used. Measurement of drug concentration will be the dependent variable.
Research Intervention(s)/Investigational Agents	Immunosuppressant tacrolimus immediate release (IR) and extended release (XR) formulation (*Envarsus® XR*)
IND/IDE # (if applicable)	Exempt
Study Population	Male and non-pregnant female kidney transplant recipients ages 18 and above.
Sample Size (number of participants)	We expect to enroll 74 patients to achieve 65 completers.
Study Duration for Individual	Six months (including pre-baseline testing)

Participants	

1.0 Objectives

1.1 Purpose: The purpose of this study is to demonstrate whether or not the extended-release tacrolimus, namely, Envarsus XR, produces fewer adverse cognitive and motor effects than the commonly used immediate-release tacrolimus formulation in kidney transplant recipients.

2.0 Background.

2.1 *Significance of Research Question/Purpose:* The calcineurin inhibitor (CNI) tacrolimus is one of the most frequently used immunosuppressants in kidney transplantation, both in early posttransplantation and as part of long-term maintenance regimens (Barraclough et al, 2011. Rostaing et al, 2016). Yet, like other CNIs, such as cyclosporine, tacrolimus is associated with numerous adverse effects including neurotoxicity, which affects approximately 10-28% of patients (Bechstein, 2000). Yet, CNI-related neurotoxicity is not well characterized, and is generally diagnosed using subjective criteria around clinical symptoms rather than objective assessments, complicating the determination of its true incidence. Typically, tacrolimus-associated neurotoxicities present as cognitive impairment, including memory deficits, tremors, altered mental status, confusion, headaches, hallucinations and/or ataxia (Cheng et al, 2012; DiMartini et al 2008), any one of which can result in a substantial reduction in the recipient's quality of life and negatively affect medication adherence. Moreover, the pathogenesis of CNI-related neurotoxicity is unclear and confounded and/or exacerbated by the presence of comorbid conditions, such as increasing age, hypomagnesemia (Thompson et al, 1984), and hypertension (Bechstein, 2000).

The cellular mechanisms underlying the adverse neurologic effects associated with tacrolimus have not been conclusively established. Tacrolimus may modulate the activity of both excitatory (NMDA) and inhibitory (GABA) amino acid receptors via calcineurin. In turn, calcineurin may modulate glutamatergic neurotransmission pre- and postsynaptically (Sander et al, 1996) as well as regulate desensitization of GABA receptors (Martina et al, 1996). Tacrolimus also inhibits the induction of long-term potentiation, which can interfere with memory acquisition (Bechstein, 2000). There is also evidence that tacrolimus causes selective toxicity of glial cells (Stoltenburg-Didinger & Boegner, 1992) and induction of apoptosis of oligodendrocytes (McDonald et al, 1996) though it not known what role these mechanisms play in the clinical manifestation of tacrolimus-related neurotoxic effects.

The lack of precise characterization of the neurotoxicities, specifically, the cognitive and motor dysfunctions associated with tacrolimus administration, as well as the gaps in our understanding of their pathogenesis severely limit the clinician's ability to reduce or prevent their occurrence. Current strategies aimed at managing these adverse events are based on the assumption that most of the symptoms are dose-related and only occur at elevated and/or peak serum tacrolimus levels blood levels (Ayres et al, 1994; Guarino et al, 1996; Bechstein, 2000; Rostaing et al, 2016). In addition, the symptoms of tacrolimus-associated neurotoxicity may be reversed in most patients by substantially reducing the dosage of immunosuppressant (Bechstein, 2000).

2.2 *Preliminary Data:* This study will, for the first time, compare cognitive and motor function in individuals placed on either an immediate- or an extended release formulation of a tacrolimus (*Envarsus® XR*) based immunosuppressive regimen, after receiving a kidney transplant. In addition to subjective measures such as the NIH PROMIS scales and the SF-12, objective assessments not previously used in the renal transplant population will be administered in order to more precisely characterize drug related cognitive and motor impairments.

2.3 *Existing Literature:* The widely used immediate-release, twice-daily capsule formulation of tacrolimus, while highly effective in preventing acute transplant rejection, has severe limitations, such as a narrow therapeutic window, interindividual variation in absorption, and low bioavailability (17% +/- 10%). *Envarsus® XR* (Veloxis Pharmaceuticals), an extended-release, once daily, tablet formulation, was developed using a proprietary drug delivery technology that critically affects drug dissolution and absorption. Consequently, *Envarsus® XR* shows a more consistent concentration-time profile over 24 hours, with reduced peak and peak-to-trough fluctuations, when compared to immediate-release tacrolimus (Rostaing et al, 2016) in de novo and stable kidney recipients similar to those participating in this study (Rostaing et al, 2016). Moreover, patients converted from immediate-release formulations to *Envarsus® XR* initially receive only 80% of prior immediate-release dosage orally once daily (Bunnapradist et al, 2013; Rostaing 2017). Therefore, compared to immediate-release tacrolimus, the extended-release formulation, *Envarsus® XR* , when taken once-daily, slows drug absorption and delivers more constant plasma concentrations with less frequent dosing, thereby potentially mitigating neurotoxic events associated with high peak drug concentrations.

Our central hypothesis is that kidney transplant recipients, when placed on a regimen of *Envarsus® XR* q.d., will experience significantly fewer adverse cognitive and motor side effects than when on a regimen of immediate release tacrolimus b.i.d.

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome: The primary objective is to compare the effect of treatment with an immediate-release tacrolimus to an extended-release tacrolimus (Envarsus® XR) immunosuppressive regiment on cognitive and motor function in kidney transplant recipients. Our primary outcome measure is the Controlled Oral Word Association (COWA: phonemic generative fluency). COWA was chosen as the primary endpoint since in previous head-to-head studies of drug-induced cognitive impairment, this measure was sensitive to the differential effects of the study drugs (Meador et al, 2003; Marino et al, 2012) including patients on calcineurin inhibitors (Syrjala et al, 2004). The primary endpoint is a change in the COWA score from baseline to each post-transplant assessment).

3.2 *Secondary Endpoint(s)/Event(s)/Outcome(s):* The secondary objective is to determine the factors that explain inter-individual variability in cognitive

response. Pharmacokinetic and demographic factors will be explored. Variability in cognitive response between individuals can be large. A population approach (nonlinear, mixed effects) will be used. Measurement of drug concentration will be the dependent variable.

4.0 Study Intervention(s)/Investigational Agent(s)

4.1 Description: The cognitive and motor effects of two FDA-approved formulations of the immunosuppressant drug tacrolimus (on-label use for kidney transplant recipients) will be evaluated: an immediate-release formulation and the extended-release formulation, Envarsus®XR.

4.2 *Drug/Device Handling:* Immediate-release tacrolimus will be prescribed by the treating physician and dispensed by the patient's pharmacy of choice. Envarsus®XR will be supplied by the sponsor, namely, Veloxis Pharmaceuticals and shipped to the Investigational Drug Services (IDS), Pharmaceutical Service, Fairview-University Medical Center, who will dispense it to patients in the XR group as prescribed by the treating physician (on- label use). Upon receipt of the study treatment supplies, the IDS staff will perform an inventory and a drug receipt log filled out and signed by the person accepting the shipment. The designated study staff will count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment will be documented in the study files. The study drug will be stored according to the stated FDA requirements as outlined in the "Storing Investigation Study Drugs" SOP dated 07/23/2003.

Regular study drug reconciliation will be performed by the study team to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

4.3 IND/IDE: EXEMPT.

5.0 Procedures Involved

Study Design: All subjects will undergo cognitive and motor function testing no earlier than two (2) months post-transplant and no later than 36 months post-transplant to become familiar with the test battery (Pre-BASELINE). The Pre-BASELINE session will take place no more than 60 days prior to the BASELINE visit. Between four (4) and 38 months post-transplant, subjects will have one blood sample taken, after which they will be administered the full battery of cognitive and motor function tests as well as self-report measures of health-related quality of life.

5.1 (Baseline). Subjects will then be randomized to remain on immediate-release tacrolimus (IR group) or switched to Envarsus XR (XR group). Both groups will have one, approximately 10-mL blood sample collected and be

administered the cognitive, motor function, and self-assessments at 6 and 12 weeks after BASELINE..

5.2 Study Procedures:

Patients participating in this study are placed on immediate-release tacrolimus immediately following transplant. Four (4) to 38 months post- transplant, half of the patients will be randomly chosen to convert to Envarsus XR, while the other half will remain on immediate release tacrolimus. Both the IR and XR formulations of tacrolimus have been approved by the FDA for use as an immunosuppressant in kidney transplant recipients and will be prescribed/dosed by the treating physician as FDA indicated.

Patients in both the IR group and the XR group will undergo cognitive and motor function testing at the following times: (1) at least Two (2) - three (3) months post-transplant (maximum 36 months post-transplant): pre-BASELINE; (2) Four (4) to 38 months post-transplant: BASELINE; (3) 6-weeks Post- BASELINE; (4) 12-weeks Post-BASELINE. Since patients on either IR or XR require therapeutic drug monitoring as part of their SOC, the blood sample taken BASELINE and at 6 and 12 weeks post-BASELINE may coincide with blood levels taken as SOC. Each visit will include a +/- seven (7) day window to increase flexibility for the subject's schedule. At each visit, subjects will be administered the following:

Executive function, processing speed, and word-level language/verbal tests:

- Phonemic generative verbal fluency will be evaluated using the COWA test. COWA requires the subject to generate words other than proper names or numbers beginning with a specific letter of the alphabet; three 60-second trials are obtained, using three different letters, usually F-A-S or B-H-R. *This is a primary Outcome Measure.*
- Symbol Digit Modalities Test (*SDMT)* is a test of psychomotor speed that requires the subject to transcribe symbols to numbers as quickly as possible with a combination of direct visual identification and short-term memorization. Symbols with empty squares are presented and the task is to fill in the corresponding number as quickly as possible. This task is timed at 90 seconds. *This is a primary Outcome Measure.*
- Semantic generative verbal fluency will be evaluated using the Animal Fluency test. Subjects are asked to generate as many different animal exemplars as they can within 60 seconds. The primary dependent measure for both phonemic and semantic generative fluency is the number of correct words meeting scoring criteria normalized to individual (averaged) baseline.
- Trails A and B will be used to assess visual search, mental flexibility, and task alternation. The subject is required to draw lines between circles in ascending order ("connect the dots"). Trail Making Part A requires the patient to connect the numbers from 1-25. Trail Making B requires subjects to alternate between numbered and lettered circles in ascending numerical/alphabetical order (e.g., 1-A-2-B, etc.) The primary dependent measure is time of completion.
- Digit span subtest from the WAIS-IV will be used to assess immediate attention. It tests forward and backward digit span, includes a sequencing trial in which the subject is the repeat back the digits in ascending order.

Computerized psycholinguistic assessment:

- Spontaneous narrative (SN) task presents the subject with an interpersonal conflict scenario (e.g., "a relative in the nursing home that is being mistreated") and is asked to explain how he/she would address the conflict in a three (3) minute speech. Different but equivalent scenarios will be used for the different study sessions to minimize practice effect.
- Picture Description task requires the subjects to describe a simple picture (e.g., The "Cookie Theft" stimulus from the Boston Diagnostic Aphasia Examination (Goodglass & Kaplan 1983).

Linguistic analysis of speech and language functioning will be performed on speech samples recorded during discourse level language/verbal tests. Both what the subjects said (*content*) and how they said it (*manner*) in response to a task such as story recall or spontaneous narrative task will be analyzed.

Motor Assessments

- Tremor will be assessed as follows: Study staff will videotape the subject while the subject performs tasks such as sitting with hands and feet relaxed, extending the arms outstretched, pointing with the fingers, pointing with the feet, pouring water (with the hands), drawing lines and spirals (with the hands), writing (with the dominant hand), holding the head upright, extending the tongue. The videos and the drawing / writing samples will be coded to ensure blinding, then rated according to the Fahn Tolosa Marin scale (Fahn et al, 1988) by a blinded rater. Videos will be stored on a University-approved encrypted server.
- Manipulative dexterity/fine motor coordination will be assessed using Grooved Pegboard Test**,** which involves placing 25 pegs as rapidly as possible into an equivalent number of similarly shaped holes, but varying in their orientation to the vertical. The primary dependent measure is the time it takes to complete the task**.**

Quality of Life Assessment

- Self-report measures of health-related quality of life will either be completed online using the brief, but highly reliable computer adapted tests of the NIH PROMIS system. [www.NIHpromis.org] or static short forms by pencil and paper. PROMIS scales will include: Physical Health (Physical function, pain intensity, pain interference, fatigue, sleep disturbance, sleep-related impairment); Mental Health (depression, anxiety); Social Health (satisfaction with social roles). These measures, along with the SF-12, will be administered at the times of the cognitive assessment and will take 15 minutes or less to complete.

Blood Draw

- One 7 to 10 mL blood sample will be collected at each visit. Over the course of the study, we will collect about 6 to 9 teaspoons of blood.
- If the subject consents to the genetic portion of the study, a portion of the baseline blood draw will be used to study specific polymorphisms that are known to affect how tacrolimus metabolizes in the body. The subject may still participate in study even if they do not consent to the genetic option.

5.3 Follow-Up: After the last study session at 12 weeks Post-BASELINE, patients who were assigned to the *Envarsus® XR* group will have the opportunity to remain on the extended-release formulation at their own expense.

6.0 Data and Specimen Banking: N/A

7.0 Sharing of Results with Participants

7.1 No results will be shared with study participants or others.

8.0 Study Duration

- We anticipate that the duration for an individual subject's participation in the study would be approximately 32 weeks.
- We anticipate it will take two (2) years to enroll all study participants.
- We anticipate it will take three (3) years from the study start date to complete all study procedures and data analysis.

9.0 Study Population

9.1 Inclusion Criteria: (1) Male or female kidney transplant recipient; (2) 18 years of age and above; (3) receiving a kidney transplant from a living or deceased donor; (4) if female, premenopausal and heterosexually active, must be using 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; (5) written informed consent to participate in the study.

9.2 Exclusion Criteria: (1) younger than 18 years of age; (2) Non-native level English speaker; (3) pregnant women (4) breastfeeding women

9.3 Screening: All patient enrollment will come from Dr. Matas' patient population. Potential subjects will be identified by information contained in their medical records. The study will be introduced either in person or by mail and either the study staff or letter will thoroughly describe the requirements of the study along with the risks and benefits of participation. Study staff will be available to answer any questions from the potential participant. If the potential participant expresses interest in participating in the study, an initial study visit will be scheduled either as a stand alone visit or concurrently with a standard of care clinic visit in order to further discuss the study, address any questions, and determine the patient's final eligibility. Also see sections *12.0* (Local Recruitment Methods) and *21.0* (Consent Process*)* for further details.

10.0 Vulnerable Populations

10.1 Vulnerable Populations: *Identify which of the following populations will be involved in this study. (You may not include members of the populations below as participants in your research unless you indicate this in your inclusion criteria above.)*

☐ Children

☐ Pregnant women/Fetuses/Neonates

☐ Prisoners

☐ Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders

☐ Non-English speakers

☐ Those unable to read (illiterate)

☐ Employees of the researcher

☐ Students of the researcher

☒ None of the above

10.2 *Adults lacking capacity to consent and/or adults with diminished capacity to consent:* N/A

10.3 Additional Safeguards: N/A

11.0 Local Number of Participants

11.1 Local Number of Participants to be Consented: Sample sized is based on the primary endpoint (COWA). In a longitudinal neurocognitive study of patient on immune suppressant drug therapy Syrjala et al (2004) found that the mean T score for the COWA (based on a population norm set at 50, with a standard deviation SD of ± 10) declined by 5 units (0.5SD) from pretransplanation to 80 days posttransplanation. Since a change of 0.5SD is considered standard clinical criteria for a medium effect size, we based our calculation of the power for the COWA upon a standard deviation of the difference score between baseline and follow up of a 5-point performance decline. Therefore, a total of 65 patients will yield a probability of 80 percent that the proposed study will detect a treatment difference of 5 units in COWA at a two-sided 0.05 significance level. To account for possible dropouts, we will recruit 74 patients.

12.0 Local Recruitment Methods

12.1 Recruitment Process: All patients of the transplant center are told by clinical staff and educators that they will likely be approached for research studies pre- and post-transplant. Given the number of studies and sheer volume of patients seen at the transplant center, specifics of each study are not discussed in great detail. This is largely due to the fact that the amount of time between referral to our transplant program, being waitlisted or

scheduled for transplant, and actually receiving a transplant can vary drastically between cases. Therefore, the initial approach for this study by the research team will occur post-transplant.

Eligible kidney transplant recipients will be initially contacted in person at a standard of care clinic visit or via mail. The ability to approach patients for the study either in person or via mail will allow the study team to capture all patients – those who routinely come into clinic for follow-up care and those who do not.

Subjects contacted in person will be approached by a member of the study team at a regularly scheduled clinic visit to discuss the study and provide potential subjects with a copy of the consent form to review. If the subject expresses interest in participating, either at that time or at a later time, an initial study visit will be scheduled where the subject will sign the consent form prior to any study procedures. Subjects approached via mail will be sent an IRB-approved invitation letter and copy of the IRB-approved consent form at least one to two months (maximum 36 months) after their kidney transplant surgery. A follow-up phone call will be made to the potential participant after an appropriate amount of time has passed for the letter and consent form to be delivered and reviewed. Study staff will call the potential participant, identify themselves as affiliated with the University of Minnesota, and explain to the potential participant why they are calling. The study will be introduced and the study staff will thoroughly describe the requirements of the study along with the risks and benefits of participation and answer any questions from the potential participant. If the potential participant expresses interest in participating in the study, an initial study visit will be scheduled either as a stand alone visit or concurrently with a standard of care clinic visit. The potential participant will sign the consent form at the initial study visit. This will allow plenty of time for potential subjects to review the consent form and consider the study. For additional information regarding the consent process, see section 21.0 of this protocol.

Potential participants may also choose to self-identify for this study. Our research group, the Surgery Clinical Trials Office (SurgCTO) has a website that lists our actively enrolling studies. This website is publicly available and can be reviewed by patients who want to know specifics about studies being conducted within the abdominal transplant division and contact information for the study team. Patients of the clinics are also referred to StudyFinder, which lists all active studies in which SurgCTO is participating and study team contact information.

12.2 Source of Participants: Participants will be recruited from the patient population SurgCTO, where the co-PI (Matas) is a practicing physician. Participants will be identified through their medical records.

12.3 Identification of Potential Participants: Potential subjects will be identified by information contained in their medical records. The principal investigator and the UMN research team have permissible access to the medical records as the co-PI (Dr. Matas) has a treating relationship with the patient population eligible for this study. All potential subjects are patients of the University of Minnesota Transplant Clinic and Nephrology group. Only internal patients are recruited for this study.

All members of the research team have access to EPIC. Within EPIC, researchers will first look at potential subjects' patient type to determine if they have opted out of research. If the potential subject has not opted out of research, preliminary screening will take place and a letter may be sent to the potential subject.

If the patient has opted out of research, the researcher will not look into the patient's chart, preliminary screening will not take place, and a letter will not be sent. If the patient comes to clinic for a standard of care appointment, the patient may be approached in person by the clinical team to ascertain interest in the study. If the patient expresses interest in the study, the researcher will inform the patient that they need to review the patient's medical record to determine eligibility. If the patient is eligible, the consent process will proceed.

12.4 Recruitment Materials: Recruitment will begin at least one to two months (maximum 36 months) after potential subjects have had a kidney transplant. A letter will be sent briefly describing the study and include contact information for the research team. The IRB-approved consent form will also be included with the letter for review. A follow-up phone call will be made to the potential participant after an appropriate amount of time has passed for the letter and consent form to be delivered and reviewed.

The recruitment letter, consent form, and script for the phone conversation will all be reviewed and approved by the IRB prior to subject recruitment. If a potential subject has a standard of care appointment at the University of Minnesota near the time he or she will be eligible for the study, study personnel may approach them in person. In that situation, the consent form will be provided to the patient to review.

12.5 Payment: Subjects will not incur costs as a result of participation in the study. Compensation will be $50 for each of the four (4) study sessions (a total of $200 if they complete all 4 visits) for their time and inconvenience. Subjects will also be eligible for up to a total of $200 in travel expenses (reimbursed at $0.535 per mile round trip) for the four (4) post-transplant visits (excluding the pre-BASELINE visit) during which they are scheduled to receive a battery of cognitive, motor function, and self-assessments. If a subject cannot continue or chooses to drop out of the study, their payment will be prorated for the sessions completed. Compensation will be issued from the University of Minnesota.

13.0 Withdrawal of Participants

13.1 Withdrawal Circumstances: Subjects will be asked to withdraw from the study if the treating physician and/or co-PI (Dr. Matas) determines that there is a reason to significantly alter the subject's drug regimen at any time during the study, including switching to an alternate immunosuppressant. Subjects who are noncompliant with study visits or who, at any time during the study, feel that they can no longer complete the neurocognitive assessment battery may also be asked to withdraw from the study.

13.2 Withdrawal Procedures: Every attempt will be made (phone calls, email) to connect to subjects who fail to appear at any visit or abruptly withdraw from the study. Once withdrawal is confirmed, an exit form will be completed, documenting the reason(s) for withdrawal. No attempt will be made to collect any data after withdrawal.

13.3 Termination Procedures: Data collected from subjects who either withdraw from the study voluntarily or who are asked to withdraw will be analyzed and retained in the database.

14.0 Risks to Participants

For each risk or set of risks below, include the procedures to be performed to lessen the probability, magnitude, duration, or reversibility of those risks.

14.1 Foreseeable Risks: 1. Possible bruising as a result of needle stick to obtain blood sample; 2. CNI-immunosuppressant therapy is SOC in this population, and there are risks associated with their use (refer to attached package inserts for both immediate- and extended-release tacrolimus). All participants will be monitored by Dr. Matas throughout this study as SOC, thus there is no added risk in switching from immediate-release to extended-release tacrolimus.

14.2 Reproduction Risks: N/A

14.3 Risks to Others: N/A

15.0 Potential Benefits to Participants

15.1 Potential Benefits: There are no direct benefits to study participation.

16.0 Data Management

16.1 Data Analysis Plan: In order to maintain conceptual control over the experiment-wise Type I error rate, we have identified our primary outcome measure as COWA. This measure was chosen because of its sensitivity to drug effects on cognitive performance (Meador et al, 2003; Syrjala et al, 2004; Marino et al, 2012). Repeated measures analysis of variance methods will be used to compare our two treatments (tacrolimus IR vs tacrolimus XR) with respect to each of the cognitive (neuropsychological and speech) assessment variables outlined previously. These outcomes will be measured at four time points (time: Baseline; 6 weeks post-Baseline; 12 weeks post-Baseline; 24-weeks post-Baseline) and treatment effect as well as order,

time, order*treatment and time*treatment interaction effects will be examined. In the event that data on any of these variables does not satisfy the assumption of normality, transformations and/or non-parametric repeated measures ANOVA alternatives such as Friedman ANOVA by ranks may be utilized. Neuropsychological and speech change scores will each be summarized within each treatment at each assessment time with means and standard deviations (and/or medians and IQRs). As exploratory work, we will also examine whether clinical covariates such as age, gender, education, and concomitant medications modify any of the neurotoxicity effects using repeated measures analysis of covariance methods. Individual cognitive outcomes will be evaluated based upon reliable change index (RCI) criteria. RCIs control for practice effects, regression to the mean, and other measurement error sources to indicate individual performance that statistically exceeds chance fluctuation. We will use a 90th percentile RCI for both our primary and secondary dependent variables. A decline of 4 points constitutes of statistically reliable decline for verbal fluency (Kockelmann et al, 2003)] and a decline of 6 points is the 90th percentile decline for SDMT (R.C. Martin, personal communication 2004; unpublished data Martin et al., 1999). The number of patients showing declines that statistically exceed the effects of test measurement error and practice will be analyzed non-parametrically using Fisher's Exact Test.

PK/PD Modeling: A pharmacokinetic (PK) pharmacodynamics (PD) approach can give insight in understanding how the body influences tacrolimus concentrations (PK step) and how variations of these concentrations influence neurocognitive performance (PD step). Single trough levels will be obtained at study visits, which in some instances may overlap with routine clinical care. Sparse sampling requires a non-linear mixed effects approach (i.e., NONMEM) that is robust with respect to missing data and sparse data sets. Covariates known to effect drug disposition in this population such as age, renal function, gender, co-medications, etc. will be included in the model building algorithms. These data will be collected from the patient medical record. PD modeling will investigate if a relationship exists between clinical covariates associated with the cognitive and motor measures (such as COWA) and drug concentration and derived measures of drug exposure.

16.2 *Power Analysis:* Sample sized is based on the primary endpoint (COWA). In a longitudinal neurocognitive study of patient on immune suppressant drug therapy Syrjala et al (2004) found that the mean T score for the COWA (based on a population norm set at 50, with a standard deviation SD of ± 10) declined by 5 units (0.5SD) from pretransplanation to 80 days posttransplanation. Since a change of 0.5SD is considered standard clinical criteria for a medium effect size, we based our calculation of the power for the COWA upon a standard deviation of the difference score between

baseline and follow up of a 5-point performance decline. Therefore, a total of 65 patients will yield a probability of 80 percent that the proposed study will detect a treatment difference of 5 units in COWA at a two-sided 0.05 significance level. To account for possible dropouts, we will recruit 74 patients.

16.3 Data Integrity: Data will be stored in REDCap, a database secured by the University of Minnesota. All data will be double entered by trained study staff. Specimens will be stored in the -80 freezer in lab 522C, 717 Delaware Street SE. Data and specimen will be kept until the completion and publication of final manuscripts. Primary investigators and study staff with proper training will have access to the data and specimens. Video (i.e., tremor assessments) and audio (cognitive testing/language) recordings will be stored on a University of Minnesota/HIPAA-approved encrypted server.

17.0 Confidentiality

17.1 Data Security: Study data will be maintained in source documents and case report forms (CRFs). Source documents will be maintained in paper and electronic formats and CRFs will be maintained electronically.

Paper source documents will be kept in research offices. Access to the research offices is restricted. The suite can only be entered via card swipe or key pad access. All subject information recorded on paper is kept in a source binder and kept within file cabinets and shelving unites within the office.

Electronic source documentation (labs, reports from physicals, etc) will either be stored in the subject EMR, EPIC, or as PDF files on the Department of Surgery's secure, encrypted server, which part of the Academic Health Center's (AHC) server. Access to all electronic data is password protected and all data are encrypted.

A copy of the consent form will be placed in subjects' medical record and study information will be included in subjects' research window in EPIC per University requirements. This is included in the confidentiality section of the study consent form.

Direct identifiers will be maintained locally both during and after this study. All documents that include these direct identifiers will only be kept locally at UMMC. Any information (CRFs or other reports) that is sent to the study sponsor will have PHI redacted.

A unique subject number will be assigned to each participant. Monitors from the study sponsor, University oversight committees, regulatory authorities (FDA), or other regulatory bodies will have access to subject source documentation with data identifying study subjects during site monitoring or auditing visits. This information is included in the "Confidentiality" section of the consent form.

The study team will maintain a key which links the study code/identification number and subject initials to the subject's name and medical record number.

No directly identifying information will be maintained longer than necessary. Written and electronic records, reports, and data will be retained on site at the UMMC as per local, or at least two years after study completion or the study is terminated, whichever is longer.

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants:

18.1 Data Integrity Monitoring**:** This study will be monitored according to GCP guidelines. The investigator will allocate time for such monitoring activities. The investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities and has adequate space to conduct the monitoring visit. Additionally, case report forms will be periodically reviewed by the study team

18.2 Data Safety Monitoring: All subjects have been recruited from Dr. Matas' patient population and have regularly scheduled clinic visits to assess their health post-transplant. Tacrolimus levels are taken by Fairview staff and they have a protocol in place if a critical result is found. If randomized to XR group, physicians follow on-label dosing and monitoring guidelines.

The monitoring plan will be conducted by the Principal Investigators and the Study Team. The monitoring plan will address the following: enrollment, adverse events, outcome data, protocol non-compliance, and new and relevant information to the study participants. Study coordinators will collect AEs and SAEs via EPIC and through conversation with the subjects during study visits. Study coordinators will record any AEs on CRFs and on CTSI provided AE log sheet. They will then report AEs and SAEs in a timely manner, according to GCP guidelines to the PIs and the IRB, when necessary. Unexpected SAEs are to be reported to the IRB at most 24 business hours after the event and expected AEs will be reported annually with the continuing reviews.

Additionally, subjects may be removed from the study if determination by the treating physician deems there is a reason to significantly alter the subject's drug regiment at any time during the study, including switching to an alternate immunosuppressant.

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Protecting Privacy: If a potential participant is approached in person, the consent discussion will take place in a private room. By discussing the study in private, no information regarding the study and subsequently the subject can be heard by others in the clinic. Distractions will be kept to a minimum.

If a potential participant is approached via mail and later by phone, the research team will verify that they are talking to the correct person over the phone. The study team will not leave messages containing PHI. If the study team leaves a message, they will only state that they are calling about study information that was sent in the mail, and ask for the potential participant to call them back.

19.2 Access to Participants: All members of the research team will have access to the participants' EMR in EPIC. Data will be extracted from the participants' standard of care treatment in the EMR, so access is necessary to obtain this information. All study participants have a treating relationship with the principal investigator, and will likely maintain a treating relationship with the co-PI, Dr. Matas, after study participation.

20.0 Compensation for Research-Related Injury

20.1 Compensation for Research-Related Injury: N/A: The cognitive, motor and subjective testing and single blood draws present minimal risk to participants, as does, in the case of those patients in the XR group, switching from the IR to the XR tacrolimus formulation, which is often done in regular clinical practice. Participants will be monitored by the co-PI, Dr. Matas.

21.0 Consent Process

21.1 Consent Process (when consent will be obtained):

As stated earlier in the application (section 12.0) the consent process, in accordance with SOP HRP-090, will begin either with a letter and the consent form sent to potential participants in the mail followed by a phone call or approaching a potential participant at a standard of care appointment in the clinic or hospital. After this initial approach, the study team will work with the subject to schedule an initial study visit. The study subject will be

encouraged to review the consent form and discuss the study with friends and family prior to the initial study visit. The time between initial approach will give subjects time to consider study participation and contact the research team with any questions.

At this initial study visit, the consent form will be reviewed in detail with the study subject in a private clinic room and any questions will be answered. Subjects will be told that participation is voluntary and they may end their participation at any time without affecting their relationships with clinical or study staff.

Subjects will be given time during the initial study visit to consider the study. If a subject joins the study, a copy of the consent form will be made and given to the subject. Study assessments will only begin after written documentation of consent is obtained.

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21.2 Waiver or Alteration of Consent Process (when consent will not be obtained): N/A

21.3 Non-English Speaking Participants: N/A

21.4 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): N/A

21.5 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: N/A

21.6 Adults Unable to Consent: N/A

22.0 Setting

22.1 Research Sites: All research activities will be performed at the University of Minnesota Medical Center in the Clinics and Surgery Center or via mail.

23.0 Multi-Site Research

N/A

24.0 Resources Available

24.1 Resources Available: SOT Registry currently has approximately 3,000 living kidney transplant recipients that were transplanted at the University of Minnesota. Many of these recipients will be eligible for the study, for which we require 65 completers.

To assist with clinical trial management, the PI is utilizing services from the Surgery Clinical Trials Office (SurgCTO). SurgCTO is a central office in the Department of Surgery at the University of Minnesota designed to support the management and conduct of clinical research while promoting compliance. This is accomplished through standardizing the approach to clinical research across various divisions in the Department of Surgery, supporting investigators through regulatory and operational assistance, and providing enhancements in study management and oversight. SurgCTO will

provide assistance with study coordination and project, regulatory, data, and financial management of the trial.

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