PROTOCOL HUM NUMBER: HUM00198148
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PROTOCOL TITLE
Single center, pilot evaluation of home-based therapeutic drug monitoring for tacrolimus and mycophenolate in kidney transplantation

SHORT TITLE
Home-based Therapeutic Drug Monitoring in Kidney Transplantation

Initial version:	4/16/2021
Amended:	1/7/2022
	8/4/2022
	3/7/2023

NOTE: To effectively manage **restrictions** put in place during public health or civil emergency or restrictions **(**i.e. COVID-19 pandemic**)** changes to protocol-required items **are to be made** to minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g., to limit exposure to infectious pathogens). These changes are listed in **Appendix A** of the protocol (**Contingency Operation Plan**).

TABLE OF CONTENT

ABBREVIATIONS

AE	Adverse Event
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
DBS	Dried blood spot
IRB	Institutional Review Board
LC-MS/MS	Liquid Chromatography with tandem mass spectrometry
MOP	Manual of Procedures
PI	Principal Investigator
PO	per os/by mouth/orally
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TDM	Therapeutic drug monitoring

STUDY SYNOPSIS

Title	Single center, pilot evaluation of home-based therapeutic drug monitoring for tacrolimus and mycophenolate in kidney transplantation
Study Description	Part 1: Clinical validation of bioanalytical assay Part 2: Prospective, randomized, pilot evaluation of a text messaging intervention to facilitate self-collection of dried blood samples for tacrolimus and mycophenolate therapeutic drug monitoring
Study Duration	Part 1: 3 days Part 2: Enrollment duration: 3 months (up to 4 months if participating in qualitative interview) Subject follow-up duration: 0 months Overall study duration: 24 months
Study Center(s)	Single-center University of Michigan
Objectives	Evaluate tools to facilitate patient self-collection of samples for therapeutic drug monitoring of tacrolimus and mycophenolate including the self-collection device (Tasso-M20) and text messaging reminders.
Number of Subjects	Part 1: 45 (up to 90 if participants do not provide 2 sample, need to obtain 90 paired samples (Tasso vs. venipuncture) for approprirate statistical power) Part 2: 45
Disease/condition	Part 1: Solid organ transplant recipients requiring immunosuppression with tacrolimus and mycophenolate Part 2: Kidney transplantation requiring immunosuppression with tacrolimus and mycophenolate
Inclusion/Exclusion Criteria	See Section 3.0 for a complete list of inclusion and exclusion criteria
Description of Study Intervention:	Part 1: No intervention. Subjects will collect capillary samples using the Tasso-M20 and Mitra dried microsampling devices concurrently with their clinically indicated venipucture. Part 2: All subjects will obtain self-collected dried blood spots for analysis of tacrolimus and mycophenolate using the Tasso-M20 device (Illustrated below). On two separate days approximately 6 weeks apart. Subjects will be randomized to two text messaging interventions to provide reminders and guide collection of samples in the home environment.

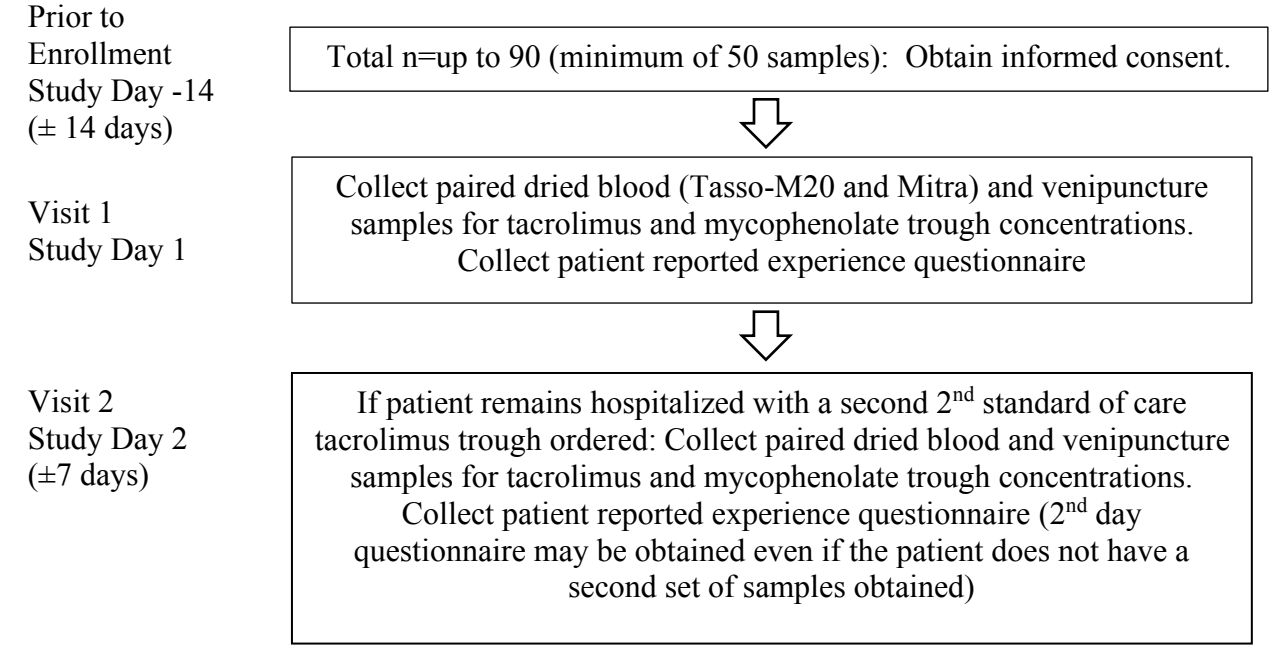
	No changes will be made to the subjects' treatment based on data collected in this study. All changes to the medication regimen will be made at the treating provider's discretion.
Duration of Intervention	Part 1: no intervention (sample collection duration up to 2 days) Part 2: 3 months
Statistical Methodology	Part 1: Bioanalytical method agreement will be assessed by Passing-Bablok regression and Bland-Altman plots. Part 2: The primary outcome is successful to home collection of samples. Multivariable logistic regression will be used to identify participant characteristics associated with successful home collection.

Illustration of the Tasso-M20 dried blood samples collection kit (A) that includes self-placement on the upper arm (B) followed by activation (clicking the red button), timed collection (C), and automatic sealed storage of four samples in a cartridge (D) for bioanalysis

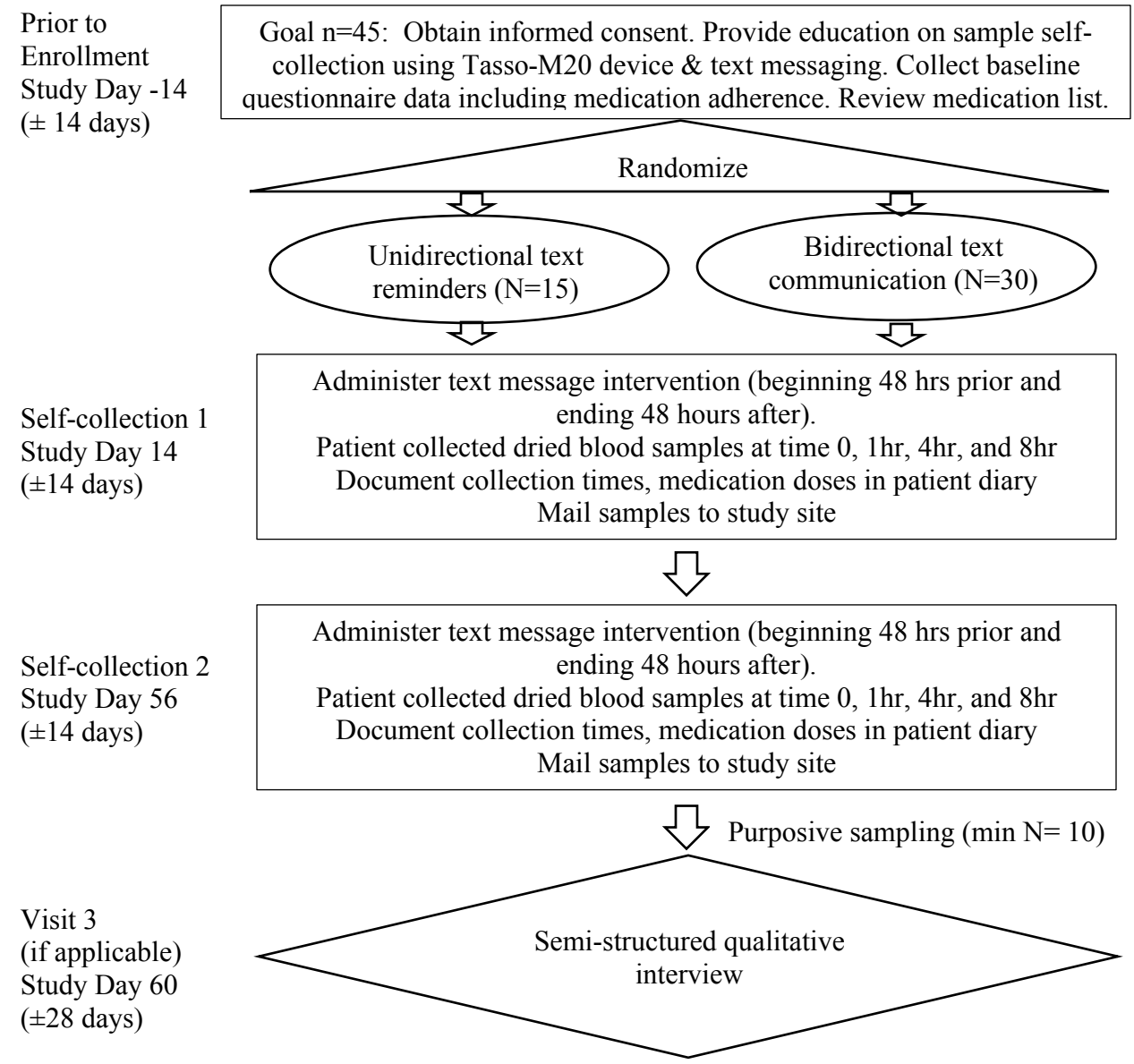
Illustration of the Mitra dired blood sample collection kit (A) that requires sampling from the capillary via fingerstick with the sample time for bioanalysis (B)

STUDY SCHEMA

Part 1:



Part 2:


Prior to Enrollment Study Day -14 (± 14 days)
Goal n=45: Obtain informed consent. Provide education on sample self-collection using Tasso-M20 device & text messaging. Collect baseline questionnaire data including medication adherence. Review medication list.
Randomize
Unidirectional text reminders (N=15)
Bidirectional text communication (N=30)
Self-collection 1 Study Day 14 (±14 days)
Administer text message intervention (beginning 48 hrs prior and ending 48 hours after).
Patient collected dried blood samples at time 0, 1hr, 4hr, and 8hr
Document collection times, medication doses in patient diary
Mail samples to study site
Self-collection 2 Study Day 56 (±14 days)
Administer text message intervention (beginning 48 hrs prior and ending 48 hours after).
Patient collected dried blood samples at time 0, 1hr, 4hr, and 8hr
Document collection times, medication doses in patient diary
Mail samples to study site
Purposive sampling (min N= 10)
Visit 3 (if applicable) Study Day 60 (±28 days)
Semi-structured qualitative interview

1.0 BACKGROUND AND RATIONALE

1.1 Background

Optimal immunosuppression therapy is critical for kidney transplantation success. The care of transplant recipients has improved remarkably over the last 50 years, and transplantation offers a clear survival benefit, higher quality of life, and lower cost than dialysis.[1-4] Yet, 10-year all-cause graft failure remains high at approximately 50%. This number corresponds to many recipients requiring a second or third transplant, whereas, for others, it represents premature death from cardiovascular disease, infection, and malignancy.[2, 5] Importantly, the cause of negative transplant outcomes can often be traced in some capacity to immunosuppression, and optimization of the drug regimen has the potential to improve long-term graft and patient survival.[6-8] New therapeutic options have failed to emerge, and the standard of care immunosuppression of tacrolimus and mycophenolate has not changed in nearly 20 years. Current practice is limited in its ability to balance the prevention of immune-mediated graft damage with the development of adverse side effects. Dose modifications remain reactive and primarily based on clinical evaluation and trough concentrations of tacrolimus, which does not adequately allow preemptive identification of patients at risk. As a result, precision pharmacotherapy, enhanced pharmacokinetic (PK) monitoring, and assessment of the alloimmune response are considered research priorities by both transplant professionals and patients.[9, 10]

These observations have led to the pursuit of expanded therapeutic drug monitoring (TDM) encompassing pharmacokinetic monitoring of drug exposure by estimating area under the concentration-time curve (AUC) for both tacrolimus and mycophenolate and evaluation of potential immune biomarkers. In several studies, estimating AUC has better correlated with reductions in acute rejection.[11-15] Similarly, valganciclovir/ganciclovir, a commonly received antiviral, displays larger inter- and intra-patient PK variability. A reported 50 to 80% of patients do not achieve therapeutic exposure with current dosing recommendations.[16] This is particularly relevant in kidney transplantation where low and fluctuating GFR is common in the post-operative period; subtherapeutic exposure is most common when adjusting the dose based on the current manufacturer recommendations for altered kidney function. Unfortunately, AUC is also the PK parameter associated with ganciclovir efficacy and toxicity.[17] Additionally, relationships with several immune biomarkers (e.g., donor-derived cell-free DNA, NFAT-regulated gene expression) and outcomes have also been identified with evidence supporting use as pharmacodynamic markers.[18] Monitoring concentrations of metabolites, such as mycophenolic acid glucuronide, may also be beneficial as they offer insight into metabolic capacity and are hypothesized to be associated with toxicity but are incompletely studied.[19] Further knowledge of the impact of enhanced TDM remains needed to confirm optimal AUC targets and establish the best biomarker strategy to classify subclinical immune activity in large, prospective, longitudinal clinical trials. Finally, widescale implementation in practice is hampered by the perceived complexity compared to trough concentration monitoring. The full realization of the therapeutic potential will remain difficult in the absence of new tools to increase the translatability by reducing cost and patient burden.

1.2 Rationale

Forward progress in precision dosing using AUC and biomarker monitoring is hindered by the logistics of adequately powered, prospective studies. Home-based therapeutic drug monitoring (TDM) using volumetric dried blood microsampling to collect multiple concentration-time points for Bayesian AUC estimation and immune biomarker analysis is an innovative, practical, *and* cost-effective approach that could be used to implement precision dosing for both future studies and clinical practice.[20-22]

Collection of dried capillary blood is a minimally invasive method for in-home use where patients self-collect small blood samples. Dried blood samples have been used for nearly a decade to obtain specimens for immunosuppression concentrations but can be limited by extraction recovery, hematocrit effect, and sample quality.[23-28] Volumetric, whole sample analysis has the potential to mitigate these problems. Volumetric sampling has been used successfully to obtain immunosuppression and ganciclovir concentrations in several small studies.[20, 29-32] The next generation collection device, Tasso-M20 (Tasso Inc, Seattle WA), offers precise volumetric sampling with the potential to improve patient satisfaction and acceptability by offering a near painless experience but has not yet been used in transplantation. The device includes a self-contained lancet that obtains four 20 µL dried capillary samples from the upper arm during a single, button-activated collection event (Figure 1).

Figure 1.
Tasso-M20 Device

In transplantation, existing literature suggests patients can collect dried blood samples at home, are generally satisfied with the procedure, and are willing to provide more samples with this method, particularly if it can replace venipuncture or reduce clinic visits.[22, 24, 27, 31, 33] However, data are primarily limited to non-US populations and lack a robust framework to ensure a complete understanding of the behavior. Further, preliminary data shows that adherence to the collection is low, with 42-55% completion rates without intervention.[22, 27] Additional work is needed to develop strategies to increase adherence to monitoring. Text messaging reminders have been demonstrated to improve medication adherence and other positive health behaviors.[34] Text messages are low cost with minimal infrastructure requirements and more accessible to patients with a low technology literacy or in rural areas with low cellular bandwidth. In a 2015 survey of kidney transplant recipients, 96% owned a mobile phone and 74% used text messaging compared to 47% who used apps.[35] Text messaging is the preferred method of health communication in adolescent and young adult recipients.[36] The use of text messaging offers the potential to be a viable tool to increase adherence to home-based TDM for most of the transplant population.

Our contributions are expected to develop a patient-centric strategy to allow frequent, longitudinal, minimally invasive sample collection for bioanalysis of immunosuppression and other supportive therapy drug concentrations. These contributions will be significant because they are expected to overcome many barriers that have limited progress towards enhanced precision pharmacotherapy in transplantation. The methods will facilitate decentralized multicenter clinical trials by reducing costs and simplifying biorepositories to achieve the sample sizes necessary to conclusively establish the benefits of expanded TDM on long-term patient outcomes. Further, improving the technical capacity of home-based sampling to substitute for frequent phlebotomy will improve patients' quality of life by allowing increased autonomy to self-monitor by collecting blood samples at home.

2.0 STUDY DESIGN, OBJECTIVES AND OUTCOME MEASURES

This will be a single center, randomized, pilot evaluation of a text messaging intervention to facilitate self-collection of dried blood samples for tacrolimus, mycophenolate, and val/ganciclovir therapeutic drug monitoring. Particpants are not required to be receiving val/ganciclovir for participation but the concentration will be analyzed if the drug is concommitently being received by the participant under the direction of the treated clinical team.

2.1 Primary Objective (Part 2)

2.1.1 To compare the effect of bidirectional text communication on adherence to and accuracy of home-based AUC collection versus unidirectional text reminders in kidney transplant recipients receiving tacrolimus and mycophenolate.

Primary Outcome Measure: successful home-based TDM defined as the timely receipt of samples that are adequate for pharmacokinetic analysis.

2.2 Secondary Objectives (Part 1)

2.2.1 To assess the bioanalytical agreement of two sample collection methods (dried blood spot and venipuncture) as measured by Liquid Chromatography with tandem mass spectrometry (LC-MS/MS).

Secondary Outcome Measure: difference between drug concentrations measured from concurrent dried blood spot and venipuncture samples.

2.3 Exploratory Objectives

2.3.1 To evaluate the predictive performance of a mycophenolate matrix conversion equation. (Part 1)

Exploratory Outcome Measure: median percentage predictive error and median absolute predictive error

2.3.2 To assess the bioanalytical agreement of two sample collection methods (dried blood spot and venipuncture) as measured by LC-MS/MS assay at the University of Michigan PK Core and Michigan Medicine Clinical laboratory. (Part 1)

Exploratory Outcome Measure: difference between drug concentrations measured from the two LC-MS/MS assays.

2.3.3 To evaluate participant characteristics based on the Theoretical Domains Framework associated with successful home-based TDM. (Part 2)

Exploratory Outcome Measure: The relationship between patient characteristics and successful home-based TDM

2.3.4 To evaluate differences in participant reported experiences between the Tasso-M20 device and Mitra device (Part 1)

Exploratory Outcome Measure: difference between patient reported experience scores associated with the two sample collection devices

3.0 SUBJECT ELIGIBILITY

Subjects must meet all of the selection criteria to be enrolled in the study. Study treatment may not begin until a subject has provided informed consent and meets the eligibility criteria.

Part 1:

3.1 Inclusion Criteria

1. Recipient of a solid organ transplant
2. Male or Female adult (≥ 18 years)
3. Receiving tacrolimus and mycophenolate
4. Ability to understand and willingness to sign a written informed consent

3.2 Exclusion Criteria

1. Hemoglobin <8 g/dL
2. History of allergy to tape adhesives

Part 2:

3.3 Inclusion Criteria

1. Recipient of a kidney or kidney/pancreas transplant
2. Male or Female adult (≥ 18 years)
3. Receiving immediate release tacrolimus and mycophenolate mofetil
4. Participant is willing to receive text notifications and has a mobile device capable of receiving texts
5. Ability to understand and willingness to sign a written informed consent.
6. Ability to understand, read, and speak English.

3.4 Exclusion Criteria

1. Recipient of a multi-organ transplant (other than pancreas).
2. History of allergy to tape adhesives

Subjects may participate in both part 1 and part 2. Subjects participating in part 1 expressing interest in part 2 will approached again once stable in the outpatient setting. Partipiants will sign separate consent for each part of the study.

4.0 SUBJECT SCREENING, ENROLMENT, AND RECRUITMENT

A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be initially documented on a Screening and Enrollment Log.

It is the responsibility of the investigator to determine subject eligibility prior to enrollment. After subject eligibility has been determined, a signed statement (i.e. eligibility checklist) by the investigator attesting eligibility will be included in the subject file. In addition, source documentation supporting each eligibility criteria will be placed within the subject file.

4.1 Subject Recruitment and Retention

Part 1: Participants will be recruited from the inpatient transplant surgery service. Potentially eligible participants will be approached by the study team during admission to consider participation. For living donor transplant recipients, the study team may also approach potential participants during their History and Physical appointment typically scheduled 7-10 days before surgery.

Part 2: Participants will be recruited from the outpatient kidney transplant clinic at Michigan Medicine. Potentially eligible participants will be sent a letter describing the study and inviting the patient to contact the study team and/or the study team will contact participants via telephone if not attending clinic visits in person. The letter will be sent to the home address in a sealed envelope. Patients may also be approached during clinic visits to discuss the study. An incentive payment of $20 will be provided for completion of each study visit or home collection (participants may receive a total of $60). Patients may also be contacted via telephone to enhance retention if expected samples are not received.

Women and minorities will be recruited using the same strategy and are expected to be recruited at a rate consistent with their incidence in the transplant population at the University of Michigan.

4.2 Screen Failures

For part 1: Screen failures are defined as particpants who consent to participate in the clinical trail but do not subsequently have at least 1 set of paired samples obtained.
For part 2: Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of

Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) will not be rescreened. Screen failures will be replaced.

4.3 Randomization

Part 1: no randomization
Part 2: 45 patients who meet the inclusion criteria will be randomized in a 1:2 allocation ratio to receive one of two text messaging interventions stratified by age ≥ or < 65 years. The randomization list will be generated by the study biostatistician.

4.4 Blinding

Part 2: As subjects will be aware of the frequency and type of text messages received, blinding of patients is not possible. As a result, baseline data will be collected prior to randomization. Additionally, purposive sampling for qualitative interviews requires the investigator to be unblinded to study group.

5.0 INTERVENTION PLAN (PART 2 ONLY)

5.1 Intervention Administration

All participants will self-collect dried blood samples using the Tasso-M20 device at the specified intervals. Each self-collection will obtain up to 80µL of capillary blood (4 x 20µL samples). Dried blood samples will be obtained concurrently with venipuncture samples at study visit 1 and 2. The participants will self-collect dried blood samples in their home environment for AUC analysis on two occasions. Self-collected samples will be collected immediately prior to the morning dose of tacrolimus and mycophenolate (C0) and at approximately 1, 4, and 8 hours after the dose.

To promote adherence and accurate sample collection, participants will be randomized to 1 of 2 automated text messaging interventions. Messages will be sent using a commercial web to text messaging gateway (Twilio). Twilio will be enabled in the REDCap project. Message replies will be stored in REDCap not on Twilio servers. The request inspector will be disabled in Twilio as required by REDCAP for HIPPA compliance. No protected health information (PHI) or identifying information will be in messages (See Table 1 for message content). A control group without messages will not be used due to preexisting knowledge of low rates of completion without intervention.

Anticipated sample collection dates and times will be discussed with the participant during the baseline visit to trigger messaging timeline.If a response is received to any message not using an expected keyword, the recipient will receive a text message that the entery is an invalid value and to try again. The partipciants will be educted to contact the study team with any issues.

The participant will be able to opt-out of messages with the standard keywords: “cancel”, “stop”, “end”, “quit”, “stopall”, and “unsubscribe.” In response they will receive the following message: “You have successfully been unsubscribed. You will not received any more messages from this number. Someone from the study team will contact you to follow up. Reply START to resubscribe.

In response to the keywords “help” or “info” participants will receive the following message: “For help, please call the study team (734) 647-1281 or email aleino@umich.edu.”

Upon completion of study visit 3 and all study blood sample collections, a subset of patients will be selected for semi-structured qualitative interviews to further explore the home-based TDM process. The interview guide is provided in Appendix C and is informed by the Theoretical Domains Framework mapped to the Capability-Opportunity-Motivation and Behavior system. Patients will be selected using maximum variation purposive sampling to capture multiple perspectives, including those demonstrating extremes in adherence, self-efficacy, diabetes status, and time post-transplant.

5.2 Immunosuppression Dosage and Administration

Participants will continue their prescribed regimen of oral tacrolimus and mycophenolate. No changes will be made to the subject’s medication therapy as part of the study. The participant will continue their own supply of medication provided by their local pharmacy. Medication will not be supplied by the study. Dose adjustments may be made by the treating provider based on standard of care laboratory results or as determined by the treating provider to be clinically indicated. Dose adjustments will be documented in the study record.

The investigator will promote compliance by instructing the subject to take the study drug exactly as prescribed and by stating that compliance is necessary for the subject’s safety and the validity of the study. The subject should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed. If vomiting occurs within 2 hours after administration of the dose on a sample collection day, the patient may be asked to repeat the collection at a later date at the discretion of the investigator. Adherence to the immunosuppressive regimen will be monitored using patient self-report and patient diary review.

5.3 Concomitant Medications/Treatments

Concomitant medications will be administered per institution standard of care. Concomitant medication is defined as any prescription or over-the-counter preparation including vitamins and supplements. Concomitant medications will be recorded at the time of consent and visit 2 during part 2 of the study.

5.4 Duration of Study Involvement

Part 1: Study participant may continue for up to 7 days or until one of the following criteria apply:

- Subject's immunosuppressive regimen no longer includes tacrolimus and mycophenolate
- Subject voluntarily withdraws
- Study completes the study assessments (2 paired sample collections)
- Subject is discharged
- Subject hemoglobin falls below 8g/dL

Part 2: The intervention may continue for 26 weeks or until one of the following criteria apply:

- Subject's immunosuppressive regimen no longer includes tacrolimus and mycophenolate.
- Subject voluntarily withdraws from treatment
- Subject transfers care from the Michigan Medicine
- Subject completes the required study assessments OR
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator

5.5 Off Intervention Criteria

Subjects will be removed from the protocol intervention when any of the criteria listed in Section 5.4 apply. Document in the source the reason for ending the protocol and the date the subject was removed from the protocol. All subjects who discontinue treatment should comply with protocol specific follow-up procedures as outlined in Section 5.7. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely.

5.6 Duration of Follow-Up

Due to the minimal risk and nature of the intervention participants will not be followed beyond the completion of study visits.

5.7 Off Study Criteria

Subjects may request to withdraw from the study at any time, or they may be withdrawn at the discretion of the investigator for safety, behavioral, or administrative reasons. Prior to study withdrawal, participants may be asked if they are willing to complete the end of study survey and be considered for participation in the qualitative interview regarding their experience.

The reason(s) for discontinuation from study will be documented and may include:

1. Subject withdraws consent (termination of treatment and follow-up);
2. Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment;
3. Subject is unable to comply with protocol requirements;
4. Treating physician judges that continuation on the study would not be in the subject's best interest;

5. Lost to Follow-up. If a research subject cannot be located for 3 months, the subject may be considered "lost to follow-up." All attempts to contact the subject during the three months must be documented;
6. Termination of the study by The University of Michigan
7. Subject completes protocol treatment and follow-up criteria.

5.8 Subject Replacement

Part 1: Enrolled subjects may be replaced if paired samples are not successfully obtained on at least one occasion.

Part 2: Enrolled subjects may be replaced if they do not attempt at least one at-home blood collection.

6.0 STUDY PROCEDURES AND EFFICACY ASSESSMENT

6.1 Study Procedures and Assessments

This section contains a list and description of the study evaluations.

Part 1:

- During study visits 1 and 2 the following specimens will be collected for study purposes:
  - One 6-mL red top tube
    - One will be sent to the Michigan Medicine clinical laboratory for determination of mycophenolic acid and mycophenolic acid glucuronide concentration from serum. The results will be reported in the electronic medical record and will be available to the patient's clinical care team.
  - Four 20-µL capillary dried blood samples via Tasso-M20 device for determination of tacrolimus, mycophenolic acid, mycophenolic acid glucuronide, and ganciclovir (if applicable) concentrations by the University of Michigan PK Core. These results will be considered investigational and will not be shared with the patient or care team.
  - Two 20-µL capillary dried blood samples via Mitra device for determination of tacrolimus, mycophenolic acid, mycophenolic acid glucuronide, and ganciclovir (if applicable) concentrations by the University of Michigan PK Core. These results will be considered investigational and will not be shared with the patient or care team.

Standard of care labs will also be drawn at this time and processed by the Michigan Medicine clinical laboratory. Results for hemoglobin, hematocrit, albumin, and tacrolimus concentration will be collected from the electronic medication record for study purposes.

Study staff will collect any remaining/leftover blood from the Michigan Medicine clinical laboratory for additional analysis in the University of Michigan PK Core.
Participants will also complete self-report questionnaires describing and comparing the sample collection methods (Appendix B)

Part 2:

- Demographics including height and weight: will be recorded as reported by the patient or documented in the electronic medical record during the screening visit.
- Education on Tasso device utilization and diary documentation will occur after consent has been obtained at the baseline visit (may be the same day as consent). Education will be provided in a private space (such as clinic room) if completed in person. Education may also be conducted virtually at time where the patient can secure privacy.
- Biological specimen collection and laboratory evaluations:

    - During home-collection 1 and 2 the following specimens will be collected for study purposes:
        - Four 20-µL capillary dried blood samples via Tasso-M20 device will be obtained at 4 time points (0, 1, 4, and 8hrs after morning tacrolimus/mycophenolate administration). A total of 320 µL will be collected during each home-collection These samples will be used for determination of tacrolimus, mycophenolic acid, mycophenolic acid glucuronide concentrations by the University of Michigan PK Core. These results will be considered investigational and will not be shared with the patient or care team.
        - The Tasso-M20 device will be provided to the patient prior to each sample collection via US mail. The patient will also be provided with a pre-paid mailer to return the samples to the study site.
        - Each collection day will require four Tasso devices (one for each time point). The devices will be numbered to facilitate patient use.

The results of any study-specific laboratory evaluations completed by the PK core will not be used to adjust medication therapy or be provided to the participant. The mycophenolate trough concentrations in addition to the standard of care labs processed by the Michigan Medicine Clinical lab will be available in the electronic health record for review by the participant.

- Administration of study instruments for subject-reported outcomes (Appendix C):
    - During the Baseline visit participants will complete questionnaire packet 1 which includes:
        - PROMIS Self-efficacy: Managing Medications/Treatments (8 items)[37]
        - Medical Outcomes Social Support Scale (19 items)[38]
        - Transplant Effects Questionnaire (worry, guilt, disclosure, and responsibility) (18 items)[39]
        - Kidney Transplant Understanding Tool (abbreviated to the 20 items related to medication therapy and monitoring)[40]
    - During the home collections 1 and 2 participants will complete the study diary which includes:
        - Medication dose times for the 48 hr prior to collection

        - Sample collection times
    - During the home collections 1 and 2 participants will complete ecological momentary assessments via text message
        - Pain intensity
        - Interruption in daily routine
        - Difficulty of sample collection
        - 48 hours after sample collection safety will be assessed via text message
    - At end of study participants will complete questionnaire packet 2 which includes:
        - Self-reported adherence assessment
        - Acceptability and Feasibility of Implementation Measure (8 items)[41]
    - During visit 3 selected participants will participate in a semi-structured qualitative interview. The interview guide is provided in Appendix D.

6.2 Safety/Tolerability

Patients will complete ecological momentary assessments to document the participants experience by rating pain intensity, interruption in daily routine, and difficulty on a scale of 0 to 10 at the time of each Tasso sample collection. Forty-eight hours after sample collection participants will be asked if they experienced any adverse events including bruising, bleeding, and/or signs of infection. Analyses will be performed for all subjects who provided at least one blood sample.

6.3 Time and Events Table

Part 1:			
Visit Description	Screening	Visit 1	Visit 2*
Time point	Day 0	Day 1	Day 2
Visit Window	±14 days		± 7 days
Eligibility	X		
Hgb/Hct[a]		X	X
Tacrolimus trough[a] (venipuncture-clinical lab)		X	X
Tacrolimus trough[b] (venipuncture- PK Core)		X	X
Tacrolimus trough (capillary, Tasso & Mitra- PK Core)		X	X
Mycophenolate trough (venipuncture- clinical lab)		X	X
Mycophenolate trough[b] (venipuncture- PK Core)		X	X
Mycophenolate trough (capillary, Tasso & Mitra- PK Core)		X	X
Ganciclovir concentration[c] (venipuncture- PK core)			
Ganciclovir concentration[c] (capillary, Tasso & Mitra- PK Core)			
Questionnaire		X	X

*Visit 2 will occur if the following criteria are met:

1. Patient remains admitted to the hospital and study inclusion criteria continue to be met
2. A second standard of care tacrolimus trough concentration is ordered by the clinical team

Failure to collect samples for visit 2 will not be considered a protocol deviation.

[a]Hgb/Hct and tacrolimus trough values from the clinical lab will be obtained from standard of care labs

[b]Analysis will only be completed if leftover blood is available to be obtained from the clinical lab after completion of all ordered/standard of care labs

[c] Analysis of ganciclovir will only be completed if the participant is receiving ganciclovir or valganciclovir as part of their standard of care. Adidtion of ganciclovir to the analysis will not change the volume of blood collected.

Visit Description	Screening	Baseline	Home collect 1	Home collect 2	Visit 3[a]
Time point	Day -14	Day 0	Day 14	Day 56	Day60
Visit Window	±14 days	±14 day	±14 days	±14 days	±28 days
Informed Consent	X				
Demographics	X				
Eligibility	X				
Height/Weight	X				
Randomization		X			
Education		X			
Tacrolimus AUC (capillary- PK Core)[b]			X	X	
Mycophenolate AUC (capillary- PK Core)[b]			X	X	
Questionnaire 1		X			
Questionnaire 2				X	
Concomitant Medication Review	X				
Study Intervention[c]			X	X	
Drug Adherence Assessment				X	
Subject Diary			X	X	
Ecological Momentary Assessments			X	X	
Qualitative interview					X

a. Visit 3 is only applicable to participants selected using maximum variation purposive sampling
b. Consists of 4 collection events over 8 hours on each occasion (time 0, 1 hr, 4hr, and 8hr after the morning dose of tacrolimus and mycophenolate)
c. Text messaging will begin 48 hours prior to the sample collection event and continues for 48 hours after sample collection

7.0 ADVERSE EVENTS

This is a pharmacokinetic study, but safety data will be collected on adverse and serious adverse events.

7.1 Adverse Event Reporting Requirements

Since the responsibility of the management of the patient's transplant regimen is retained by the health care providers at the University of Michigan Transplant Center and not dictated by the study protocol, deaths and hospitalizations will typically not be study related. Serious adverse events (SAEs) and adverse events (AEs) that are related to the participant's kidney transplant or other chronic disease conditions are not unanticipated and therefore will not be considered reportable to the IRB. For the sake of our study purposes and outcomes we will track SAEs and AEs related to study participation.

Adverse event data will be reviewed by the project leadership team and will be summarized in reports quarterly. Non-serious (mild/moderate) adverse event data will be reported to the IRB in annual renewals. SAEs related to study participation will be reported to the IRB within 7 calendar days of identification by the study team. A privacy violation or breach of confidentiality will be reported to the IRB within 7 calendar days and to the Corporate Compliance office within 24 hours of identification.

Definition of Adverse Events (AEs): AEs that are of particular interest to our study and that we will specifically track include problems associated with capillary sampling (infection, bruising, and bleeding at the site of lancet puncture) and text message communication (privacy breach). Capillary sampling AEs will be assessed at 48 hours after collection via text message requesting patients to self-report (Table 1). We will also assess for hospitalizations, urgent care/emergency room visits, and death. These events will be collected via electronic record review or self-report.

The severity or grade of an adverse event may be measured using the following definitions:

Mild: Noticeable to the subject, but does not interfere with subject's expected daily activities, usually does not require additional therapy or intervention, dose reduction, or discontinuation of the study.

Moderate: Interferes with the subject's expected daily activities, may require some additional therapy or intervention but does not require discontinuation of the study.

Severe: Extremely limits the subject's daily activities and may require discontinuation of study therapy, and/or additional treatment or intervention to resolve.

The investigator or co-investigator is responsible for assignment of attribution.

Definite – The AE is clearly related to the study intervention.
Probable – The AE is likely related to the study treatment/intervention.
Possible – The AE may be related to the study treatment/intervention.
Unlikely – The AE is doubtfully related to the study treatment/intervention.
Unrelated – The AE is clearly NOT related to the study treatment/intervention.

7.2 Reporting of Unanticipated Problems

There are types of incidents, experiences, and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs. Unanticipated problems that are related to the study and indicate risk to subjects and are not also SAEs will be reported the IRB within 14 calendar days.

Unanticipated problem: Per FDA Procedural Guidance for Clinical Investigators, Sponsors, and IRBs (January 2009), an unanticipated problem is defined as a serious problem that has implications for the conduct of the study (requiring a significant and usually safety-related, change in the protocol (such as revising inclusion/exclusion criteria or including a new monitoring requirement), informed consent or investigator's brochure).

Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience, or outcomes is considered unanticipated if it meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency);
2. Related or possibly related to participation in the research; and
3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

Unanticipated problem Reporting: Per 21 CFR 312.66, 312.53 (c)(1)(vii), and 56.108(b)(1), should an Unanticipated problem occur during the investigation, the investigator will promptly report all unanticipated problems involving risks to human subjects or others to the IRB.

7.3 Reporting of Pregnancy

Pregnancy status will not be assessed during this study. The interventions of this study are not expected to cause pregnancy-related harm.

Participants enrolled in this study are receiving mycophenolate as the standard of care and not as a study intervention. Women of childbearing potential receive education on the risk of mycophenolate during pregnancy at the time of therapy initiation as mandated by the US Food and Drug Administration (FDA) Mycophenolate Risk Evaluation and Mitigation Strategy (REMS). Participants of childbearing potential will be provided with reinforcement of the REMS education during the informed consent process. If pregnancy occurs and mycophenolate is discontinued at the discretion of the treating physician, the study intervention will also be discontinued as stated in section 5.4.

8.0 DEVICE INFORMATION

The Tasso OnDemand is a sterile, disposable, integrated capillary blood collection device, including a lancet assembly and a detachable reservoir for the collection of blood.
The Tasso-M20 is used for the self-collection and storage of capillary blood from minimally trained users and shipping to a central laboratory for analysis. This configuration is available commercially and is registered with the FDA as a class 1 blood collection and container system. Tasso, Inc has validated the device utilizing the safety, sterility, packaging, and biocompatibility test methods required by the FDA for a medical device that interfaces with the body for less than 24 hours.

The mechanism is very simple to operate and enables the collection of a blood sample at the press of button. The device is placed on the skin of the upper arm and remains in position using an adhesive backing. The device is actuated by pressing the central button, causing an internal spring to contract and a plunger, containing a single 16-gauge stainless-steel lancet which penetrates 2.5mm into the skin. Upon actuation of the device, the lancet penetrates the skin, is immediately retracted (does not remain deployed for the whole wear time), and locks in an inactive position to prevent re-use. The lancet puncture causes blood to pool on the surface of the skin, which is further enhanced by the small amount of vacuum (~40 kPa). The base of the device is designed to collect the blood pooling on the surface of the skin and channel the blood into a detachable reservoir. The blood collection is stopped after the blood reaches an indicator on the reservoir (fill window for the dried blood configuration for a total sample of 80µL).

Risk analysis has been performed in accordance with ISO 14971. Risk Management Report Risks associated with use of the Tasso OnDemand are expected to be similar to those of other blood collection device, including risks related to the infection, pain and loss of sample integrity. The 40 kPa vacuum enhances the blood draw while reducing negative effects on the skin, such as hematomas or marks. Typically, a small mark, similar to those left by fingerstick devices, remains on the skin for 24-48 hours. Rarely, slight bruising is observed that does not lead to other negative consequences. The device presents minimal risk to the subjects in the study as the procedures involved are common lancet punctures. The device has been applied on over 50,000 subjects since 2014 without any adverse events recorded.

The Tasso-M20 is supplied to participants as part of a kit including the device in a sterile pouch, alcohol pad, bandage, instruction sheet, specimem bag/return pouch with moisture absorpting packs, and box for mailing. Each device is single use.

The Mitra is a separate specimen collector for the storage and transport of biological fluids. To obtain the capillary blood, a sterile single use, contact activiated safety lancet will be used.

9.0 STATISTICAL CONSIDERATIONS

This section presents a summary of the planned statistical analyses.

9.1 Study Design/Study Outcome Measures

Part 1: This study is a clinical validation for the comparison of bioanalytical methods.

Part 2: This study is a prospective, randomized, pilot evaluation of a text messaging intervention to facilitate self-collection of dried blood samples for tacrolimus and mycophenolate therapeutic drug monitoring.

9.2 Primary Objective (Part 2)

9.2.1 To compare the effect of bidirectional text communication on adherence to and accuracy of home-based AUC collection versus unidirectional text

reminders in kidney transplant recipients receiving tacrolimus and mycophenolate.

Primary Outcome Measure: successful home-based TDM defined as the timely receipt of samples that are adequate for pharmacokinetic analysis.

Samples will be considered timely if post-marked within 48 hours of planned sample collection. Samples will be considered adequate for analysis if all 4 sample collections are documented within the designated sample collection window.

9.3 Secondary Objectives (Part 1)

9.3.1 To assess the bioanalytical agreement of two sample collection methods (dried blood spot and venipuncture) as measured by Liquid Chromatography with tandem mass spectrometry (LC-MS/MS).

Secondary Outcome Measure: difference between drug concentrations measured from concurrent dried blood spot and venipuncture samples.

9.4 Exploratory Objectives

9.4.1 To evaluate the predictive performance of a mycophenolate matrix conversion equation. (Part 1)

Exploratory Outcome Measure: median percentage predictive error and median absolute predictive error

9.4.2 To assess the bioanalytical agreement of two sample collection methods (dried blood spot and venipuncture) as measured by LC-MS/MS assay at the University of Michigan PK Core and Michigan Medicine Clinical laboratory. (Part 1)

Exploratory Outcome Measure: difference between drug concentrations measured from the two LC-MS/MS assays.

9.4.3 To evaluate participant characteristics based on the Theoretical Domains Framework associated with successful home-based TDM. (Part 2)

Exploratory Outcome Measure: The relationship between patient characteristics and successful home-based TDM

9.5 Sample Size and Accrual

Part 1: The expected LC-MS/MS assay coefficient of variation (CV) of >5% with a range ratio of >25 requires 40 participants with 80 paired dried and venous samples (2 pairs from each participant) to clinically validate the assay, including validation of the anticipated

mycophenolate conversion factor.[42, 43] To account for participants unwilling to provide additional samples, up to 90 participants may be enrolled.

Part 2: Compared to the previous rate for successful sample collection of 55% reported in the literature, the selected sample size of 45 participants will provide this pilot study >90% power to detect a 25% difference in successful sample collection (anticipated overall success of 80% in both groups).

The sample size is also adequate to assess the secondary and exploratory outcomes. Additionally, the 45 participants will provide 80% power for a 95% confidence interval to identify a 10-point difference in the absolute prediction error (APE) between AUC calculated from all 4 samples and estimates using different sampling combinations for tacrolimus. Finally, the convenience sample of the included patients will be used for the quantitative analysis to provide preliminary data describing the relationships between Theoretical Domain constructs and successful competition of home-based TDM. Qualitative interviews will be conducted with a minimum of 10 participants or until data saturation is reached.

Subjects will be considered evaluable if they complete the baseline survey and attempt to complete at least 1 home AUC collection.

9.6 Data Analyses Plan

9.6.1 **Primary Objective**- To compare the effect of bidirectional text communication on adherence to and accuracy of home-based AUC collection versus unidirectional text reminders in kidney transplant recipients receiving tacrolimus and mycophenolate.

Primary Outcome Measure**:** successful home-based TDM defined as the timely receipt of samples that are adequate for pharmacokinetic analysis.

Samples will be considered timely if post-marked within 48 hours of planned sample collection. Samples will be considered adequate for analysis if all 4 sample collections are documented within the designated sample collection window.

The primary endpoint between the study groups will be compared using the chi-squared test. Comparisons of demographic and clinical characteristics between successful and unsuccessful participants will be made. A multivariable logistic regression will also be completed, where the primary independent variable is the study group, controlled for age, sex, and time since transplant. The latter analyses will explore factors that may impact adherence to sampling.

9.6.2 **Secondary Objectives** - To assess the bioanalytical agreement of two sample collection methods (dried blood spot and venipuncture) as measured by Liquid Chromatography with tandem mass spectrometry (LC-MS/MS).

Secondary Outcome Measure: difference between drug concentrations measured from concurrent dried blood spot and venipuncture samples.

Passing-Bablok regression will be used to measure the linear relationship between the drug concentrations obtained in venipuncture and dried capillary samples. Bland-Altman plots will be used to assess agreement and estimate bias. Acceptance criteria will be in accordance with the Food and Drug Administration (FDA) Bioanalytical Method Validation.[42] Drug concentrations from dried blood spots must be within ±15% of venipuncture value in ≥67% of samples.

9.6.3 **Exploratory Objectives**

a. To evaluate the predictive performance of a mycophenolate matrix conversion equation.

Exploratory Outcome Measure: median percentage predictive error and median absolute predictive error

The predictive performance of the anticipated mycophenolate matrix conversion equation will be estimated using the median percentage predictive error (MPPE) and median absolute percentage predictive error (MAPE) to provide measures of bias and imprecision.

b. To assess the bioanalytical agreement of two sample collection methods (dried blood spot and venipuncture) as measured by LC-MS/MS assay at the University of Michigan PK Core and Michigan Medicine Clinical laboratory.

Exploratory Outcome Measure: difference between drug concentrations measured from the two LC-MS/MS assays.

Passing-Bablok regression will be used to measure the linear relationship between the drug concentrations obtained in venipuncture and dried capillary samples. Bland-Altman plots will be used to assess agreement and estimate bias. Acceptance criteria will be in accordance with the Food and Drug Administration (FDA) Bioanalytical Method Validation.[42] Drug concentrations from dried blood spots must be within ±15% of venipuncture value in ≥67% of samples.

c. To evaluate participant characteristics based on the Theoretical Domains Framework associated with successful home-based TDM.

Exploratory Outcome Measure**:** The relationship between patient characteristics and successful home-based TDM

For the quantitative analysis, the dependent variable will be successful home-based TDM defined as the timely receipt of samples that are adequate for pharmacokinetic analysis. The survey constructs, reminder group, and patient demographics will be independent variables compared between groups. For the qualitative analysis, an abductive approach to data coding will be taken using the Theoretical Domain Framework, but themes identified outside of the framework will be further developed. Method triangulation of interview and survey data will be conducted. Joint Display principles will be applied to integrate the results.[57]

10. DATA AND SAFETY MONITORING

As this study utilizes capillary blood sampling obtained via lancet (similar to monitoring done by patients undergoing self-monitoring of blood glucose) and reminder text messages with no PHI identifiers in conjunction with standard transplant management by the patients' established treating health care provider, this study is expected to pose no greater than minimal risk and therefore a data safety and monitoring board will not be used.

Participants will be asked about adverse events following sample collection as outlined previously. The text messages logs will be reviewed at the time of anticipated responses by the study team for complications requiring intervention.

The study team will meet at least quarterly to discuss matters related to:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (Serious Adverse Event & Adverse Event reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

11. QUALITY ASSURANCE AND AUDITS

a. Audits and Inspections

A regulatory authority may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the study staff must immediately inform IRB, Medical School Regulatory Affairs, and MIAP.

b. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report major deviations within 7 calendar days of identification of the protocol deviation to the IRB. A major deviation is defined as that may adversely impact safety of participants

or a pattern of minor protocol deviations which suggest a systematic problem that may place subjects or others at greater risk of harm. Other minor deviations will be reported to the IRB at the time of continuing review. Missed or out of window laboratory collections will not be considered deviations as one objective of this study is to understand the feasibility of this approach in real world settings where patients may modify their lab collection schedule against the advice of their medical provider. Out of window collection of study specific labs are not expected to influence patient safety. The timing of labs in relation to the study window is included as an outcome variable. Patients whose anticipated sample is not received within the study window will be contacted via telephone by study staff to obtain the sample in an effort to maintain sample size for the secondary and exploratory aims but will be classified as unsuccessful for the primary endpoint. If samples from home collection 1 are still not received after the initial call, the patient will not be contacted again until after the 2nd scheduled home-collection to allow for a washout period to assess the adherence with the second set of text messages.

12. REGULATORY

a. Institutional Review Board (IRB)

Before implementing this study, the protocol, the proposed informed consent form, and other information to be provided to subjects, must be reviewed and approved by a properly constituted IRB. Any amendments to the protocol must be reviewed and approved by the IRB.

b. Subject Information and Consent

Study team member will explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent will be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it and will be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the subject could not read or sign the documents. No subject can enter the study before his/her informed consent has been obtained.

To support patient preference and reduce travel burden, consent can be completed in-person or remotely. If done remotely, to ensure participants have the opportunity for discussions with the study team a video conference (Zoom Health) or telephone call will be used prior to documenting consent. Participants will be reminded to use a private location to help ensure privacy and confidentiality during the discussion. Electronic informed consent using SignNow will preferentially be used for all participants to facilitate remote consent. Following completion, participants will be provided a signed copy of the

consent via email or mail (as requested by the participant). If participants are unable to use SignNow, they will be provided with the informed consent via mail, email, or other method. The participant will return the signed informed consent form in the manner most feasible for them, including by mail, fax, email, or as an electronic image. Upon receipt of the signed document, the study team member will also sign the document, document the informed consent was obtained, and mail or email the completed, signed form to the participant.

The informed consent form is considered to be part of the protocol and will be submitted for IRB approval.

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14.APPENDICES

Appendix A: Contingency Operation Plan

The following changes may be implemented and/or adapted without causing a deviation during a public health or civil emergency or restrictions. HOWEVER, the usual protocol parameters must be reinstated when the emergency is over or whenever local authorities and policies permit.

It is important that specific information explaining the basis for missing data be recorded in the case report forms (indicating the relationship to the event/restrictions, as applicable).

i. New subject enrollment
Together with the study supporter University of Michigan, the Sponsor-Investigator will evaluate the new benefit/risk for subjects on the trial and determine if study enrollment needs to be partially or completely paused.

ii. Study visit schedule
The following adjustments will be permissible per clinician/subject discretion and institutional/government allowance:

- Virtual or phone visits with the investigator will be allowed for all study visits.
- Collection of samples are to be performed per clinician/subject discretion and lab facility capacity/capabilities. The study visit window will be extended by 90 days or until the participant's provider deems laboratory assessment is clinically indicated.

iii. Laboratory testing
It may be possible that lab closure is required as a contingency measure during the course of a public health or civil emergency or restrictions. Should that occur:

- Blood samples will not be collected unless they can be stored.
- Patients will be allowed to have routine standard of care labs drawn at a local lab. The remaining specimen from the EDTA tube mailed to the University of Michigan for tacrolimus analysis per standard of care will be obtained for secondary use and analysis of tacrolimus concentrations by the PK Core.

iv. Informed Consent Form (ICF)
Consenting can be done virtually and digital signatures are allowed.

The study staff should communicate all changes to the research plan to the subject, as applicable, and must do so if the changes might affect the subject's willingness to continue participation in the study. Communication can occur virtually or via an addendum to the informed consent as required by the IRB. If discussed, documentation of the discussion and the subject's decision to continue/discontinue should be documented in the subject's record.

v. Statistical Analytics Plan:

Should changes in the contingency operation plan and/or protocol lead to amending the statistical analysis plan for this study, consideration for doing so will include submission and/or consultation with the applicable committees and regulatory agencies for review.

The plan for protocol deviations related to public health or civil emergency or restrictions will be assessed as part of the pre-specified analyses, and statistical procedures for handling these deviations will be addressed in the statistical analysis plan prior to database lock. Revisions to the statistical plan will be updated in the protocol and/or the statistical analysis plan, as required.

vi. Monitoring

Planned on-site monitoring visits may not be possible if the restrictions put in place limit travel and/or access to site location. As such, remote monitoring will be performed as necessary to maintain the defined monitoring schedule.

vii. Safety and Protocol Deviation Reporting

All safety and protocol deviation reporting for the study remains in place, per protocol requirements. Documentation of required reporting timelines are to be utilized during monitoring.

Appendix B. Study Instruments for subject-reported outcomes in Part 1

We are interested in your own personal views of your experience having your blood sampled with the Tasso-M20 and Mitra devices..

First, we'd like you to think about how painful each sample method was to you. Indicate on a scale of 1 to 10, where 1 is no pain to 10 is the worst imagineable pain

How painful was sampling from the **vein (venipuncture)**?

①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩
No pain									Worst pain

How painful was sampling from the **finger (Mitra)**?

①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩
No pain									Worst pain

How painful was sampling from the **arm (Tasso)**?

①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩
No pain									Worst pain

Please rank the pain from most painful (1) to least painful (3) loaction.

____ Vein (venipuncture)

____Finger (Mitra)

____Arm (Tasso)

If you had to have multiple blood samples in a single day to monitor your immunosuppression, how many samples would you be willing to collect using each method (0 samples to 24 samples)?

Number of samples with the Tasso_____

Number of samples with the Mitra_____

Number of samples from the vein_____

Now, we would like you to think about using these tools to collect blood samples to monitor your drug levels by yourself or with the help of your caregiver at home. Please indicate the extent to which you agree or disagree with these statements by ticking the appropriate box.

First, we will ask about the Tasso-M20 self-collection tool. This tool samples from your arm.

	Completely disagree	Disagree	Neither agree nor disagree	Agree	Completely agree
1. I think that I would like to collect my own samples frequently using the Tasso	①	②	③	④	⑤
2. I found the Tasso self-collection tool uncessarily complex	①	②	③	④	⑤
3. I think the Tasso self-collection tool would be easy to use	①	②	③	④	⑤
4. I think I would need the support of a technical person (like a nurse or phlebotomist) to be able to use the Tasso self-collection tool	①	②	③	④	⑤
5. I found the various functions in the Tasso tool were well integrated	①	②	③	④	⑤
6. I thought there was too much inconsistency with the Tasso tool	①	②	③	④	⑤
7. I imagine most people would learn to use the Tasso self-collection tool very quickly	①	②	③	④	⑤
8. I found the Tasso self-collection tool to be very cumbersome to use	①	②	③	④	⑤
9. I feel very confident that I could use Tasso the self-collection tool	①	②	③	④	⑤
10. I would need to learn a lot of things before I could get going with the Tasso self-collection tool	①	②	③	④	⑤

Now think about using the Mitra tool. The Mitra tool samples the blood from a fingerprick.

	Completely disagree	Disagree	Neither agree nor disagree	Agree	Completely agree
1. I think that I would like to collect my own samples frequently using the Mitra	①	②	③	④	⑤
2. I found the Mitra self-collection tool uncessarily complex	①	②	③	④	⑤
3. I think the Mitra self-collection tool would be easy to use	①	②	③	④	⑤
4. I think I would need the support of a technical person (like a nurse or phlebotomist) to be able to use the Mitra self-collection tool	①	②	③	④	⑤
5. I found the various functions in the Mitra tool were well integrated	①	②	③	④	⑤
6. I thought there was too much inconsistency with the Mitra tool	①	②	③	④	⑤
7. I imagine most people would learn to use the Mitra self-collection tool very quickly	①	②	③	④	⑤
6. I feel very confident that I could use Mitra the self-collection tool	①	②	③	④	⑤
7. I would need to learn a lot of things before I could get going with the Mitra self-collection tool	①	②	③	④	⑤

Which tool would you prefer?	Tasso (arm)	Mitra (finger)	Neither, I prefer sampling from my vein

Finally, we would like your thoughts about collecting drug levels at home overall.

	Completely disagree	Disagree	Neither agree nor disagree	Agree	Completely agree
1. Home collection of drug levels meets my approval.	①	②	③	④	⑤
2. Home collection of drug levels is appealing to me.	①	②	③	④	⑤
3. I like home collection of drug levels.	①	②	③	④	⑤
4. I welcome home collection of drug levels.	①	②	③	④	⑤
5. Home collection of drug levels seems implementable.	①	②	③	④	⑤
6. Home collection of drug levels seems possible	①	②	③	④	⑤
7. Home collection of drug levels seems doable.	①	②	③	④	⑤
8. Home collection of drug levels seems easy to use.	①	②	③	④	⑤

Do you already have experience with pricking yourself (for example with a blood glucose or INR measurement?) Yes No

Do you have any other comments or thoughts about the self-collection tools?

_____

_____

Appendix C: Study instruments for subject-reported outcomes in Part 2

We are interested in your own personal views of how you *now* see your experience with your kidney transplant. These are statements other people have made about their transplant experience. Please indicate the extent to which you agree or disagree with these statements by ticking the appropriate box'.

	Completely disagree	Disagree	Neither agree nor disagree	Agree	Completely agree
With regard to my transplant I feel that I am carrying around something fragile.	①	②	③	④	⑤
I am hesitant to engage in certain activities because I am afraid of doing harm to my transplant	①	②	③	④	⑤
I am worried about damaging my transplant	①	②	③	④	⑤
I monitor my body more closely than before I had the transplant	①	②	③	④	⑤
I worry each time my anti-rejection drug regimen is altered by my doctor	①	②	③	④	⑤
I keep wondering how long my transplant will work	①	②	③	④	⑤
I do not have any feelings of guilt toward the donor	①	②	③	④	⑤
I feel guilty about having taken advantage of the donor	①	②	③	④	⑤
The donor had to suffer to make me feel better	①	②	③	④	⑤
Sometimes I think that I have 'robbed' the donor of a vital part	①	②	③	④	⑤
I have the feeling that the donor/the donors' family has some control over me	①	②	③	④	⑤
I am uncomfortable with other people knowing that I have a transplant	①	②	③	④	⑤
I have difficulty in talking about my transplant	①	②	③	④	⑤
I avoid telling other people that I have a transplant	①	②	③	④	⑤
Sometimes I think I do not need my anti-rejection medicines	①	②	③	④	⑤
Sometimes I forget to take my anti-rejection medicines	①	②	③	④	⑤
I find it difficult to adjust to taking my prescribed anti-rejection drug-regimen	①	②	③	④	⑤
When I am too busy, I may forget my anti-rejection medicines	①	②	③	④	⑤

Sometimes I do not take my anti-rejection medicines	①	②	③	④	⑤
I think that I have a responsibility to the transplant team to do well	①	②	③	④	⑤
I feel that I owe the donor/the donor's family something that I will never be able to repay	①	②	③	④	⑤
I think that I have a responsibility to the donor/the donors' family to do well	①	②	③	④	⑤
I think that I have a responsibility to my friends and my family to do well	①	②	③	④	⑤

People sometimes look to others for companionship, assistance, or other types of support. How often is each of the following kinds of support available to you if you need it? Choose one number from each line.

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
Someone you can count on to listen to you when you need to talk	①	②	③	④	⑤
Someone to give you information to help you understand a situation	①	②	③	④	⑤
Someone to give you good advice about a crisis	①	②	③	④	⑤
Someone to confide in or talk to about yourself or your problems	①	②	③	④	⑤
Someone whose advice you really want	①	②	③	④	⑤
Someone to share your most private worries and fears with	①	②	③	④	⑤
Someone to turn to for suggestions about how to deal with a personal problem	①	②	③	④	⑤
Someone who understands your problems	①	②	③	④	⑤
Someone to help you if you were confined to bed	①	②	③	④	⑤
Someone to take you to the doctor if you needed it	①	②	③	④	⑤
Someone to prepare your meals if you were unable to do it yourself	①	②	③	④	⑤
Someone to help with daily chores if you were sick	①	②	③	④	⑤
Someone who shows you love and affection	①	②	③	④	⑤
Someone to love and make you feel wanted	①	②	③	④	⑤
Someone to who hugs you	①	②	③	④	⑤
Someone to have a good time with	①	②	③	④	⑤
Someone to get together with for relaxation	①	②	③	④	⑤

Someone to do something enjoyable with	①	②	③	④	⑤
Someone to do things with to help you get your mind off things	①	②	③	④	⑤

Please respond to each question or statement by choosing one box per row that describes your CURRENT level of confidence.

CURRENT level of confidence…	I am not confident at all	I am a little confident	I am somewhat confident	I am quite confident	I am very confident
I can follow directions when my doctor changes my medications	①	②	③	④	⑤
I can take my medications when I am working or away from home	①	②	③	④	⑤
I can take my medications when there is a change in my usual day (unexpected things happen)	①	②	③	④	⑤
I can manage my medication without help	①	②	③	④	⑤
I can remember to take my medication as prescribed	①	②	③	④	⑤
I can use technology to help me management my medications and treatments (for example: to get information, avoid side effects, schedule reminders)	①	②	③	④	⑤
I can list my medications, including the doses and schedule	①	②	③	④	⑤
I can figure out what treatment I need when my symptoms change	①	②	③	④	⑤

This next section ask you to answer some question about kidney transplant. Please fill out the questions as honestly as you can and do not look up any of the answers. Your responses are confidential, and the results will in no way impact your care.

TRUE OR FALSE: CHOOSE THE BEST ANSWER

1. Transplant pills must be taken to help prevent rejection.

□ True □ False

2. Anti-rejection medications are also called immunosuppressants.

□ True □ False

3. You should always take your anti-rejection medications unless instructed by your transplant team.

□ True □ False

4. You will need to do blood testing at least every 3 months for as long as the kidney transplant is functioning.

□ True □ False

5. Herbal supplements are generally safe to take with your transplant, since they are natural.

□ True □ False

CHECK THE CORRECT ANSWERS (YOU MAY CHOOSE MORE THAN ONE)

6. When thinking about herbal or traditional therapies, which of the following are true? (check all the correct answers)

___ Traditional treatments are safe for a kidney transplant because they are natural.

___ Herbal medications recommended in the media (i.e., internet, TV) are generally safe for your transplant.

___ Pills that boost your immune system are safe for people with a transplant.

___ Family and friends may suggest herbal remedies or natural products - you should check with your transplant team before trying them out.

7. Which statement are true regarding anti-rejection medication (check all the correct answers)

___ Anti-rejection pills increase the risk of infection.

___ Anti-rejection pills can be stopped if the kidney transplant is working well in ten years.

___ Anti-rejection pills increase the risk of cancer.

___ Anti-rejection pills can be stopped if side effects are too bad.

___ Anti-rejection pills can sometimes be changed if side effects are too bad.

8. If you are experiencing a side effect from your anti-rejection pills, what should you do? (check all the correct answers)

___ Continue taking the pills as prescribed.

___ Contact your transplant team.

___ Decrease the dose of your anti-rejection pills to see if that helps.

___ Stop your anti-rejection pills until you can see your doctor.

___ Try to manage the side effects with over the counter medications.

9. It is important to tell all your doctors that you received a kidney transplant because: (check all the correct answers)

___ Other pills may not mix well with anti-rejection pills.

___ Anti-rejection pills make it easier for you to catch infections.

___ Anti-rejection pills increase your cancer risk, so regular checkups are important.

___ Some pills may harm your transplant.

___ Anti-rejection pills may affect how you heal after surgery.

___ You do not need to tell your doctors that you have a transplant.

10. It is important to tell your pharmacist that you received a kidney transplant because: (check all the correct answers)

___ Other pills may not mix well with anti-rejection pills.

___ Your pharmacist can help you decide if you should treat common problems (like heartburn or (cold sores) with over the counter medications.

___ Some over the counter medications can harm your transplant.

___ You do not need to tell your pharmacist that you have a transplant.

11. When thinking about transplant rejection, which of the following are true? (check all the correct answers)

___ Rejection cannot be treated.

___ Stronger anti-rejection pills can sometimes treat rejection.

___ You have a good match, so rejection cannot occur.

___ If you take your anti-rejection pills correctly, rejection will not occur.

___ You will know if you have rejection because you will feel sick.

12. Years after your kidney transplant, which of the following are true? (check all the correct answers)

___ Some anti-rejection pills can hurt the kidney transplant.

___ High blood pressure can hurt the kidney transplant.

___ More pills may be needed to treat complications from the transplant.

___ Your transplant team may decrease your anti-rejection pills.

___ Your transplant team may need to increase your anti-rejection pills.

We are interested in your own personal views of your experience using the Tasso-M20 device to obtain blood samples yourself. Please indicate the extent to which you agree or disagree with these statements by ticking the appropriate box.

	Completely disagree	Disagree	Neither agree nor disagree	Agree	Completely agree
1. Home collection of drug levels meets my approval.	①	②	③	④	⑤
2. Home collection of drug levels is appealing to me.	①	②	③	④	⑤
3. I like home collection of drug levels.	①	②	③	④	⑤

4. I welcome home collection of drug levels.	①	②	③	④	⑤
5. Home collection of drug levels seems implementable.	①	②	③	④	⑤
6. Home collection of drug levels seems possible	①	②	③	④	⑤
7. Home collection of drug levels seems doable.	①	②	③	④	⑤
8. Home collection of drug levels seems easy to use.	①	②	③	④	⑤

Appendix D: Interview Guide

Table 3. Interview Guide for patients related to the Theoretical Domains Framework[44-48]

COM-B Component	Domain	Interview Item
Capability	Knowledge	Why is it important to monitor your immunosuppression?
		Tell me about how and when you obtain blood samples to monitor your immunosuppression.
		Do you know what your target tacrolimus level is?
		Can you give me some examples of what can increase or decrease your tacrolimus level?
		Would having more knowledge about why your transplant team asks that you obtain samples to monitor your immunosuppression make it more likely you'd be willing to collect the samples? What about collecting one sample vs multiple samples?
	Memory, attention and decision processes	Is remembering to obtain samples to monitor your immunosuppression ever an issue? How often do you forget?
		Will you remember to obtain samples? How? Were the reminders helpful? What else would be helpful?
		How much attention will you have to pay to obtain samples at home vs the lab?
		When might you decide to not obtain samples? Would this be different if you could obtain more samples at home?
		Would you be willing to continue to obtain the multiple samples in the same day? What would make you more or less willing? What about increasing how often you obtain samples (i.e. obtain home samples monthly, lab q3)?
	Behavioral regulation	Do you keep track of your overall kidney health including tacrolimus level?
		Are you aware of your day-to-day behavior as you work to keep your kidney healthy?
		Are there procedures or ways of thinking that would encourage home monitoring?
	Skills	How helpful was the training you received on how to obtain blood samples at home? What would make it better?
		How easy or difficult was it to obtain the samples at home? What problems did you encounter? What would help?
		Do you know how to check your results via the online portal?
		What additional skills do you or your fellow transplant recipients need to obtain samples at home?
Opportunity	Environmental context and resources	Are there competing tasks or time constraints to monitoring? Do you think this would change if you could obtain samples at home and have fewer visits to the lab?

		Where did you obtain the samples (home, work, etc)? Did anything in your environment affect whether you were able to obtain samples? Would you be able to do it in a different location if needed?
		Did you have the necessary resources to perform the home sampling? What resources additional resources would help?
		How did the tools you were given (sample kit and reminders) help you obtain home samples?
	Social influences	Do the people who are important to you think you should monitor your immunosuppression?
		Did the people around you ever affect your ability to obtain samples (either at home or at the lab)?
		Do you have the support from other people you need to perform home sampling? (family, friends, provider) How do these people help you? What might make their support more or less important?
Motivation	Social role and identity	Do you believe you have a responsibility to complete the recommended monitoring? Why?
	Beliefs about capabilities	How confident are you that you can obtain samples despite difficulties? (little time, conflicting demands)
		How capable would you feel if you were asked to continue to obtain samples at home? How long do you think would you feel capable?
		How well equipped did you feel to obtain the samples?
		How optimistic are you that monitoring your immunosuppression will help maintain your health?
	Beliefs about consequences	What do you think will happen if you do not complete immunosuppression monitoring? (positive/negative, short/long term)
		Do you think monitoring your immunosuppression is a good thing? Why?
		How much difference do you think more frequent or complete data on your immunosuppression levels will make in your care? Why?
		What are the costs or negative consequences of monitoring your immunosuppression? (financial, time, personal) Would home-monitoring reduce these costs? What are consequences if you do not monitor your immunosuppression?
	Motivation and goals	How much do you want to obtain samples to monitor immunosuppression? Is this different with venipuncture compared to home samples? (willing to do more with home samples?)
		How much of priority is monitoring your immunosuppression to you? What would make it more or less of a priority?
		Are there other things you want to do or achieve that might interfere with monitoring? Is this different with venipuncture compared to home samples?
		What motivates you to monitor your immunosuppression?

		For how long do you intend to monitor your immunosuppression?
		Is monitoring your immunosuppression consistent with your health goals?
	Emotion	On the days you obtain samples are you able to enjoy your normal day-to-day activities? Is this different for home vs lab?
		Does obtaining samples to monitor your immunosuppression cause an emotional response such as stress, gratefulness, or anxiety? If so, what? Why?
		To what extent do your emotions help or hinder your ability or willingness to obtain samples to monitor your immunosuppression? Is there a difference between venipuncture and home monitoring?
	Nature of the behavior/intervention	What would need to be different for you to routinely obtain home samples?
		What would be helpful to prompt you to obtain samples? (how is this different than the reminders you received?)
		How long do you think it would take you to be comfortable with obtaining samples at home?
		Would it be easier or harder to obtain samples at home versus the lab?
		What do think you is most valuable about obtaining samples at home? What about the reminders?