

PROTOCOL TITLE:

Multifaceted Intervention To Improve Graft outcome disparities in African American Kidney
Transplants (MITIGAAT)

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Specific Aims

- Aim 1. Determine the impact of this multilevel health services intervention on achieving improved adherence to tacrolimus, measured using tacrolimus trough variability and time in range in the treatment vs control arm.
- Aim 2. Determine the impact of this multilevel health services intervention on blood pressure (BP) and glucose control (in those with DM) in the treatment vs control arm.
- Aim 3. Conduct a cost-benefit analysis (CBA), assessing the estimated hospitalization and ED visit costs in the intervention arm vs the control arm and compare this to the costs needed to deliver the intervention.
- Aim 4. Compare the incidence of acute rejection, graft loss and death in the intervention patients vs. a large contemporary national cohort of Veteran kidney transplant recipients while also assessing racial disparities for these health outcomes.

2.0 Background

Racial disparities in kidney transplant is a public health issue that has persisted for more than 50 years. As compared to Caucasians, African American (AA) kidney recipients have nearly twice the risk of graft loss at 5-years post-transplant. Despite recent data demonstrating modest improvements in this disparity, a kidney transplanted today is still expected to function about half as long in AAs.¹⁻³ Marginal improvements in AAs are due to improved access to transplant, stemming from organ allocation policy changes, and reductions in early acute rejection through better understanding of immunologic risk and use of potent immunosuppression.⁴⁻⁶ However, recent studies from our team and others, demonstrate that post-transplant outcome disparities in AAs can predominately be explained by issues that arise late (≥ 2 -years) after transplant.⁸⁻¹⁰ These issues include late medication non-adherence leading to high tacrolimus variability and rejection and poor control of diabetes and hypertension.⁷⁻¹³ In models adjusting for these late issues, the risk of graft loss in AAs was reduced by up to 75%, as compared to non-AAs, and losing statistical significance.⁷⁻¹¹

For the past decade, our research team has focused on improving post-transplant outcomes and reducing disparities in AA kidney recipients by developing and using mobile health (mHealth) and telehealth interventions.¹⁴⁻²⁰ Our mHealth app and intervention are founded on self-determination theory (SDT) and designed to improve patient autonomy, competence and relatedness.²¹⁻²³ This is coupled with the use of pharmacist-led motivational interviewing (MI) delivered during televisits, designed to improve care and identify and address barriers preventing optimal adherence and comorbidity management, including medication costs.²⁴⁻²⁷ Our mHealth, telehealth intervention improves access to care through remote patient monitoring (RPM) and medication therapy management (MTM); addressing structural barriers, racial bias, and therapeutic inertia that induce disparities.²⁸⁻³⁰ Through robust preliminary research, we developed, refined, and tested the functionality, acceptance, and durability of our intervention.¹⁴⁻¹⁷ We completed a 60 patient (65% AA) pilot study (NIDDK K23DK099440) demonstrating significant improvements in the control of diabetes and hypertension through our mHealth intervention; improvements in hypertension control were more substantial in AAs.¹⁶ In 2020, we completed a 12-month randomized controlled trial (AHRQ R18HS023754) in 136 patients (64% AA) that used our mHealth, RPM, pharmacist-led telehealth intervention to improve medication adherence and reduce hospital readmissions and

costs by over 40%.^{14,20} These two clinical trials demonstrated our intervention is highly accepted in AAs; 55% of our kidney transplant population is AA, while 65% of study participants were AA. Dropout rates were 3%.^{16,20} An economic analysis demonstrated the intervention provided a net cost savings of \$368,839 through reduced hospitalizations and had a return of investment of \$4.30 for every dollar spent.³¹

The next clear step in our research trajectory is to conduct a long-term, large-scale study and assess whether this four-component health services intervention can improve health outcome disparities in AA kidney transplant recipients. Thus, we propose an RCT to use this system to deliberately address post-transplant disparities in AAs entitled the “Multifaceted Intervention to Improve Graft outcome disparities in African-American Kidney Transplants (MITIGAAT)” study. The overarching hypothesis for MITIGAAT is that late non-adherence and suboptimal control of diabetes and hypertension are more common in AA kidney recipients and are major contributors to health disparities. A multimodal intervention that addresses these issues will significantly reduce AA disparities.

3.0 Intervention to be studied

Patients randomized to the intervention arm will be provided the same usual care as the control group. In addition, these participants will receive comprehensive supplemental remote monitoring and follow-up by utilizing our smartphone-enabled mHealth app/dashboard, integrated with home-based monitoring of BPs/ glucoses and pharmacist-led scheduled televisits. Subjects in this group will be provided with a study-issued smartphone and data plan if they are not current owners of a device that is compatible with the mHealth app (iOS or Android). Subjects with compatible smartphones will be given the option to receive a study-issued smartphone and data plan. All will also be provided with a Bluetooth-enabled, automated, cuff-style bicep home BP monitor. Those with diabetes will be provided a Bluetooth enabled glucometer with testing supplies. On the mobile device, our mHealth app will be installed which displays the patient’s med list and alerts them when it is time to take each medication, requiring them to respond via push button when they have taken the specified medications, providing a time stamp of intake as part of a multi-method adherence tracking system.^{14,86} The intervention will include clinician-led telemonitoring of patient adherence to medications, appointments, BP measures, glucose readings in DMs, and EHR information (tacrolimus variability, appointments and insurance status) and 21 scheduled telehealth visits with patients that cover specific topics as detailed below (table).

Telehealth visits activities and schedule: We have a detailed plan we developed from previous work we will use for televisits in this study.^{14,20} The pharmacist will first introduce themselves and provide a synopsis regarding the call rationale. Following this, they will conduct medication reconciliation, discuss lifestyle, diet, and review home measures to determine causes of suboptimal adherence and BP/DM control. Motivational interviewing (MI) will be used to develop and implement a patient-centered plan to address these issues. The MI process used is as follows: establish rapport; assess knowledge, health literacy, motivation, and confidence; define barriers, concerns, and positive self-motivational statements about their behaviors; summarize ‘pros’ and ‘cons’ of proposed; provide options to help with adherence; and give a summary of the session,

having the patient repeat back key details. During this call, the pharmacist will implement agreed upon changes to meds and monitoring plan. This process was purposely developed so that it can be conducted during televisits.²⁴⁻²⁷ Each televisit will have a predominant theme, such as BP management, DM management, adherence, lifestyle, etc. During these 21 visits (table to the right), we will consistently use MI to better understand patient's ambivalence towards specific issues and their intrinsic motivations and values to resolve these self-contradictory factors. Culturally competent MI will be used to work collaboratively towards goals and as a means towards improved overall well-being and health. MI is well-known to our investigator team, as we have used these in our formative research and demonstrated successful outcomes.^{14,16,20} The mHealth and remote monitoring dashboard are supplemental technology-enabled tools that will help reinforce the telehealth sessions and provide the patient and team objective comprehensive data to gauge successes and continued barriers. All encounters will be documented in the EHR.^{14,20}

Smartphone mHealth application:

Through an iterative, patient-centered process, we developed, tested and validated a mHealth app that will be used within this study.¹⁴⁻¹⁸ This app was used for a recently completed RCT demonstrating efficacy in reducing medication errors and improving adherence (NCT03247322).²⁰ The app performed well and feedback from enrollees is that it was well-received and is useful to help with medication adherence and comorbidity self-monitoring and regulation.²⁰ A brief description of the app and function is as follows: After a patient logs into the app using a HIPAA-compliant PIN, they are taken to their home screen. From here, they can record and/or review medications, BPs, glucoses, and med side effects. They can also directly call the transplant center, study coordinator or pharmacy for refills, and send real-time email alerts to the clinician if they need to document a medication change, a visit to the ER, or admission to the hospital. When the patient taps the medications button, they can review their complete medication list, which is automatically updated from the EHR. Patients can review their medication regimen scheduled times and select which medications they are taking to document adherence. If the patient wants to document medication side effects, they tap the "Side Effects?" button, which brings them to the survey to document incidence and severity of side effects. To review and automatically upload (using Bluetooth) BPs and blood glucoses, the patient taps the appropriate button, which brings them to the BP or glucose page. The data from Bluetooth connected home monitoring is automatically synced to the mHealth app, encrypted, and transmitted

Months	Telehealth Visit #	Techniques Used and Topic(s) Covered
1-2	1	Teach patient how to use app and home BP and glucometer
	2	Review technology with patient, troubleshoot any issues
3-4	3	Using MI, discuss current control of HTN & barriers to optimal control
	4	Educate on importance of HTN control & implement strategies to improve self-monitoring & management
5-6	5	Using MI, discuss current control of DM & barriers to optimal control
	6	Educate on importance of DM control & implement strategies to improve self-monitoring & management
7-8	7	Using MI, discuss current control of anemia & barriers to optimal control
	8	Educate on importance of anemia control & implement strategies to improve management
9-10	9	Using MI, discuss adherence to immunosuppression & barriers to optimal adherence
	10	Educate on importance of med adherence & implement strategies to optimize adherence
11-12	11	Educate importance of staying active & implement strategies to improve staying active/exercising
	12	Educate importance of smart dietary choices & implement strategies to choose wisely
13-14	13	Review current HTN control & using MI identify barriers to optimal control
	14	Implement additional strategies to improve HTN control
15-16	15	Review current DM control & using MI identify barriers to optimal control
	16	Implement additional strategies to improve DM control
17-18	17	Review current anemia control & using MI identify barriers to optimal control
	18	Implement additional strategies to improve anemia control
19-20	19	Review medication adherence and implement strategies to improve if not optimal
21-22	20	Discuss any ongoing issues with patient precluding optimal management of comorbidities & adherence
23-24	21	Study close out session. Conduct surveys & implement plan for continued engagement

to the web-based portal. The mHealth app also provides several important and timely push notifications to patients, including when it is time to take their medications, check their BP/glucose and take a survey. The push notifications have a snooze function as well (every 30 min, up to 3 snoozes). The app provides daily individualized motivational text messages to patients, based on SDT and a comprehensive survey the patient completes at initiation.¹⁸ These messages are automated based on how well the patient is adhering to the medication regimen and monitoring. We will enhance the app by making it compatible on Android (currently only on iOS), improve the medication data from the EHR to make it real-time (currently on an overnight delay), and add surveys.

Remote monitoring dashboard: We will also utilize a web-based dashboard portal that was developed as part of the aforementioned RCT.²⁰ The system curates data from the EHR and app and presents it in summary form on a single screen, where the clinician user can efficiently review patients (each row is a single patient), sort relevant measures (each column) and identify and triage at-risk patients. Each patient row is color-coded based on risk factors. Blue demonstrates a patient with all measures within goal, yellow demonstrates a patient with one measure out of range, while red indicates two or more measures outside targets. The thresholds for out-of-range values were set based on validated levels from previous research.⁸⁻¹¹ From this portal, the clinician can also edit patient contact information, change the passwords or login credentials for the app, update the medication regimen timing, update timing of notifications to check home measurements and directly text patients. Several different reporting capabilities are available through the system; reports display trends in BPs, glucoses, and medication adherence. These data can be downloaded as raw values into a spreadsheet and shared with patients or outside providers. We will improve this current system by adding insurance status to address medication access, adjust thresholds to identify at-risk patients and add a scheduling module.

Enhanced usual care control arm: The standard care that is provided to all transplant kidney recipients will continue to be provided to both arms in this study. The structure and processes involved within this care model are well-established, as evident by our institutions ranking amongst the top-performing U.S. transplant centers for length of stay (LOS), readmissions, and outcomes. Our kidney program was bestowed the ASHP Foundation Award for Excellence in Medication-Use Safety for demonstrating improvements in outcomes through a pharmacist-led, comprehensive multi-disciplinary quality improvement initiative.⁹⁶ As part of this initiative, specific protocols, which delineate immunosuppressant regimens, laboratory evaluations and timing, follow-up clinic schedules and the treatment of comorbidities (hypertension, diabetes, hyperlipidemia) will continue to be utilized. During the long-term ambulatory care phase, patients are followed with serial labs and clinic visits as follows. From months 6 to 12 post-transplant, patients have labs every month with clinic visits every 3 months. From year 1 to 3 post-transplant, patients are seen every 6 months with labs every 2-3 months. After year 3, patients are seen annually with labs every 3 months. For the enhanced usual care arm, to ensure we have home BP and glucose measure results to compare between arms, patients will be given access to the app to use in a passive mode, meaning data will be collected, but no interventions will be delivered. Within this usual care arm, no alerts or alarms will be set within the app. If a patient does not have a compatible smartphone and/or data plan, one will be provided. All will be provided a Bluetooth-enabled BP device and glucometer (for DMs) and supplies. To minimize attention control bias, we will provide enhanced attention control as follows: Subjects in the control group will receive SMS messages every 7 days on general health-related topics. These messages include healthy lifestyle tips related to physical activity, dietary intake, non-exposure to first- or second-hand smoke, and limited alcohol intake. To address missing data, if a control patient fails to use the app or provide home measures >1 months' time, a research coordinator will contact the patient to gather this data

4.0 Study Endpoints

- **Tacrolimus variability** (Primary Outcome, Aim 1): Defined as the intrapatient tacrolimus concentration coefficient of variation (CV): standard deviation divided by the mean for each patient. All outpatient true trough tacrolimus levels drawn will be used to calculate the tacrolimus CV. We will assess every 3 months, which aligns with the minimum lab draw schedule for kidney transplant recipients at our center. This is the sole primary outcome and will be analyzed using repeated measures methodology, estimating efficacy effect size using the time*treatment interaction term and disparity using the time*treatment*race interaction term. If a patient has graft loss/death, their data will be censored at that time and still included in the analyses.
- **Time in therapeutic range (TITR, Secondary Outcome, Aim 1)**: Defined as the proportion of time the tac levels for a given patient are within desired therapeutic range, typically 6-10 ng/mL. Goal ranges may vary by patient but is well-documented in the medical record. TITR will be calculated using a modified version of the linear extrapolation Rosendaal method, as proposed by Reiffel et al. All outpatient trough tacrolimus levels will be used to calculate the TITR. We will aggregate these and assess every 3 months, analyzed using repeated measures. Effect size will be estimated using the time*treatment interaction term and disparity using the time*treatment*race interaction term. Censoring will be the same as with tac variability.
- **Medication adherence survey** (Secondary Outcome, Aim 1): Defined based on a self-reported questionnaire administered to patients in both arms through the app every 3 months (9 total, including baseline). The IMAB-Q 10 will be used; a validated, easy to administer, 10 question instrument. A score of <20 (range 10 to 50) indicates medication adherence. This is a secondary outcome; analyzed using repeated measures (estimating efficacy effect size using the time*treatment interaction term and disparity using the time*treatment*race interaction term). Censoring will be the same as for tac variability.
- **BP assessments** (Secondary Outcome, Aim 2): Defined as the mean of all systolic BPs checked by patients at home and the transplant center (ambulatory measures). Patients with a mean of SBP ≤ 140 mmHg will be considered controlled. All patients will utilize the same home-based device for these measures and taught proper technique. This will be aggregated and assessed every month (25 total); analyzed using repeated measures (time*treatment interaction term to estimate effect size and disparity using the time*treatment*race interaction term). Censoring will be the same as with Aim 1.
- **Glucose assessments** (Secondary Outcome, Aim 2): This will only be assessed in those with a diagnosis of diabetes, estimated to be more than 50% of the study population. Glucose control will be defined as the mean measure of all glucoses (random or fasting). Only those with diabetes will be included in this outcome. Those with DM and a mean random glucose ≤ 160 mg/dL will be considered to controlled. All patients will utilize the same meter and strips for these measures. We will aggregate and assess this every month (25 total); analyzed using repeated measures (time*treatment and disparity using the time*treatment*race interaction term). Censoring will be the same as with Aim 1.
- **Home-monitoring of BP and glucose adherence** (Secondary Outcome, Aim 2): The patient follows the recommended frequency of checking (through the mHealth app) home measures. The recommendation will be at least every 5 days for BP and daily for glucose (in those with DM), assessed every month and analyzed using repeated measures (time*treatment) interaction term to estimate effect size and disparity using the time*treatment*race interaction term). Censoring will be the same as with Aim 1.
- **Healthcare utilization** (Secondary Outcome, Aim 3): Defined as any hospitalization or ED visit that occurs during the study period. Assessments will be analyzing using count data

modeled using Poisson or negative binomial link. Total length of stay will also be assessed. Efficacy will be assessed by including the treatment arm and disparity using the treatment*race interaction term. Censoring will be the same as with Aim 1.

- **Hospitalizations** (Secondary Outcome, Aim 3): Defined as any admission to a hospital with at least one overnight stay. Hospitalizations that occur outside the study institution will be gathered at the end of the study by querying the South Carolina Revenue and Fiscal Affairs Office (SC RFA), which tracks all hospitalizations for South Carolinians, regardless of payer. We will use previously validated methodology to assess all cause events and to categorize cause and report hospitalizations due to med errors/ADRs.
- **ED visits** (Secondary Outcome, Aim 3): Defined as any visit to the ED with a documented encounter during the study period. ED visits that occur outside the study institution will be gathered at the end of the study by querying the South Carolina RFA, which tracks all ED visits. We will use previously validated methodology to categorize all cause ED visits as well as those due to med errors/ADRs.
- **Healthcare costs** (Secondary Outcome, Aim 3): All charge data for hospitalizations and ED visits are comprehensively gathered, regardless of payer, by the South Carolina RFA. These data will be sent to us at the end of the study, along with the encounters. This is administrative claims data, and we have experience using this dataset in previous analyses. Charges will be converted to estimated costs using the Medicare cost-to-charge ratio (CCR), published by CMS for SC, as described in the analytic plan below.
- **Intervention delivery costs** (Secondary Outcome, Aim 3): Costs uniquely tied to the delivery of this intervention will be explicitly captured; these include costs of effort from the research team and costs associated with refinement and maintenance of the biomedical informatic systems, data feeds, and mHealth application. This cost data will be compared to the cost differences produced by healthcare utilization rates in the intervention vs control arms for the cost-benefit analysis, as outlined in the analytic plan; similar to our completed R18 cost study.
- **Infections** (Tertiary Outcome): Defined as any documented infection in the medical record, either empirically treated or culture positive. Untreated upper respiratory illnesses and asymptomatic bacteriurias will not be included. Type of infection will be subcategorized as opportunistic (including CMV and BK) or not. Rates of infections will be modeled similar to healthcare utilization, with Poisson or negative binomial modeling. Efficacy will be assessed by including the treatment arm and disparity using the treatment*race interaction term. Censoring will be the same as with Aim 1.
- **Acute rejection** (Aim 4): Defined as a renal allograft biopsy showing at least grade 1A rejection by Banff criteria.^{110,111} Per usual care practices, all patients are required to have biopsy confirmation of rejection episodes within 24 hours of onset of treatment for acute rejection. It is standard care that all kidney allograft biopsies performed for transplant recipients occur at the transplant center (study institution). Biopsies will be read by a blinded local pathologist, as usual care. This will be assessed using time to event analyses. All biopsies are standard of care.
- **Graft failure and death** (Aim 4): Graft failure will be defined as return to chronic dialysis, nephrectomy, re-transplant, or death. The timing and cause of each graft loss will be recorded for comparative analysis. Patient death will also be captured, with timing and cause. These will be analyzed using time to event methodology. For primary and secondary outcomes, graft loss and death will be considered censoring events; data accrued until these events will be used in analyses.

5.0 Inclusion and Exclusion Criteria/ Study Population

- Adult (≥ 18 years) kidney transplant ≥ 2 years post-transplant that meet eligibility (see below) will be approached by researchers for consideration for participation. After discussing the details of the study, providing time, and gaining informed consent, patients will be randomized in a 1:1 fashion (blocks of 10) to either the enhanced control group (usual care + attention control) or the intervention group (usual care + 4-level intervention). For the Aim 4 cohort study, we will include all adult solitary kidney recipients transplanted between 2015 and 2021 with ≥ 2 yrs of follow-up to match the RCT.
- **Inclusion Criteria**
 - ≥ 18 years of age
 - ≥ 2 years post-kidney transplant
- **Exclusion Criteria**
 - Non-kidney transplant recipient (liver, lung, heart, intestine, pancreas, bone marrow)
 - Not capable of:
 - Measuring own BP and glucose in those with diabetes
 - Use mobile health application after adequate training
 - Speak, hear, and read English

Diversity Plan

Inclusion of Women: Approximately 55% of the participants will be women. We will not utilize sex/gender as a screening characteristic. By historical context, just over half of those that have a kidney transplant at our center are female and this is how we rationalize the 55% female sex estimate. Sex can be a strong confounder and also an effect modifier. Thus, although we will not select patients based on sex, we will assess for confounding and effect modification. We will do so by ensuring participant sex is well-captured in the dataset and included as a key variable in multivariable modeling. We will also add sex*treatment interaction terms in multivariable models for primary and secondary outcomes. Should there be any evidence of significant effect modification by sex, we will stratify models by this variable and report results and inferences separately. We will also theorize why this effect modification occurred within the discussion sections of manuscripts and reports created as part of the dissemination plan.

Inclusion of Minorities: We will not use race or ethnicity as a screening characteristic for the RCT. Any race or ethnicity will be allowed in this study. Based on our previous research, we expect approximately 50 to 55% of patients enrolled in the RCT to be African American, while the remaining 45 to 50% will be nearly all Caucasian. Using historical data from our kidney transplant center, we have very low rates of Hispanics (1-2%) and Asians (1-2%) in our kidney transplant population. Thus, for power analysis purposes, comparisons will be made between African Americans vs. non- African Americans for all disparity analyses. This is also appropriate given the formative data supporting the similarity in graft survival rates in U.S. kidney transplant recipients between Caucasians, Asians, and Hispanics. From our previous analyses, we know that

approximately 34% of patients in the national VA cohort are expected to be non-Hispanic Black (NHB). We will compare the VA NHB to the VA NHW populations for the disparity analyses surrounding the conduct of Aim 4. We will not exclude based on race or ethnicity in the VA analysis. If we have ample populations of Hispanics and Asians, we will also compare to these populations. We plan to enroll patients that are at least 18 years of age at the time the study opens, with no maximum age of enrollment for this study. This study does focus on improvement outcomes in adult kidney transplant recipients. A number of the interventions may be transferrable to adolescents, but the technology would be challenging to implement in children <13 years of age. This is one reason for excluding children from this study.

Inclusion of Children: The reason to exclude those 13 to 17 years of age is that their care is provided by pediatric nephrologists. The care of pediatric kidney transplant recipients is provided by a different group of physicians and operates under completely different care models and protocols. To minimize complexity, and because all our preliminary data come from an adult population, we will focus solely on those that are at least 18 years of age at the time of transplant. We will have no maximum age limit for eligibility. We plan to collect and report age to both the NIH in annual reports and within presentation of the results. Age groups and outcomes by groups will be assessed and reported. We will include mean age and age groupings within data safety monitoring reports as well. We will report age groups using specified categories as recommended by the NIH or CDC as appropriate. Several cognitive issues arise in aged transplant recipients and this intervention may help with forgetfulness and/or regimen complexity as factors inducing or worsening medication non-adherence. Thus, we expect the study will improve outcomes across all adults, but perhaps particularly within aged recipients. However, using technology may be a challenging issue in those of advanced age, which may also influence the impact of the intervention. Thus, we will test for both effect modification and confounding by age (see statistical analysis plan). If age is an effect modifier, we will present the results both in overall fashion and stratified by age categories that are clinically relevant (for instance, those <65 years of age vs. those ≥65 years of age). If confounding by age exists, we will ensure all model estimates are fully adjusted by age by including the appropriate functional form of age (either as a continuous variable if appropriate or by clinically relevant age categories if needed). The investigator team are well-versed at working with patients in this age range. In our previous clinical trials, we have included patients aged 18 years and above, and have ample experience and expertise in working with patients over the age of 65 years as well. More than 35% of patients in our clinical practice and previous clinical trials are aged over 65 years of age. Explain the rationale for the involvement of special classes of subjects, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations. Note that 'prisoners' includes all subjects involuntarily incarcerated as well as subjects who become incarcerated after the study begins.

6.0 Number of Subjects

For the RCT (Aims 1 through 3), we will recruit and enroll 190 participants (95 in each arm), with roughly 55% (100 participants) being African American. For the Aim 4 cohort, we will include all adult solitary kidney recipients within the VA system transplanted between 2015 and 2021 with ≥2 yrs of follow-up to match the RCT. We expect to have between 8,000 and 10,000 patients in this retrospective cohort.

7.0 Setting

MUSC will be the sole site for the RCT portion of this study. For the Aim 4 cohort, this will be a retrospective cohort with data stored in the VA CDW research environment, VINCI.

Study Sites

This is a single site study. For the RCT, only patients from MUSC kidney transplant program will be recruited and enrolled in the study. For the Aim 4 cohort study, the site will be the Ralph H Johnson VAMC through an affiliation with MUSC.

8.0 Recruitment Methods

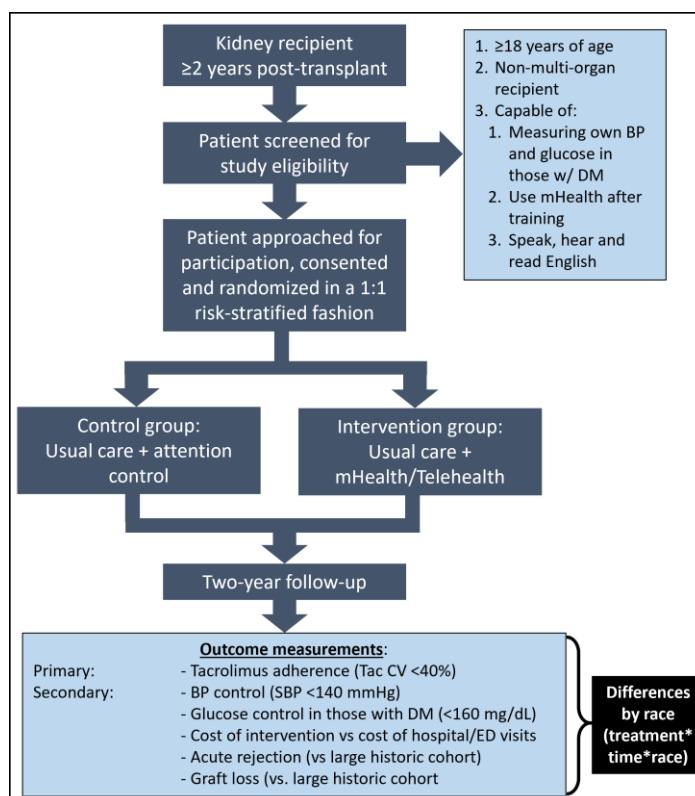
For screening and enrolling for the RCT, the study site for MITIGAAT trial is the MUSC Transplant Ambulatory Clinic, located on the 9th floor of Rutledge Tower in Charleston, SC. We will also conduct virtual screening using the MUSC kidney transplant roster. We will also be disseminating recruitment flyers, so that others who may be interested can reach out. We will conduct virtual recruitment and informed consent as well. All of the interventions for the study will occur using remote monitoring and telehealth visits, outside of the usual care clinic. If patients are recruited virtually, we will utilize the MUSC IRB template cold call script (see included appendix).

9.0 Consent Process

Patients that are screened and meet criteria will be approached (either in person in clinic or virtually) by study personnel for informed consent. This may occur during a routine clinic follow-up in the ambulatory care setting. The MUSC IRB approved consent form will be reviewed with each patient. If the recruitment occurs virtually, over the phone, or from the flyer we will utilize the MUSC IRB template cold call script (see included appendix). The study rationale and all study-related interventions and procedures will be reviewed with the potential participant. All questions will be answered, and patients will be given adequate time to review the information, including the consent documentation. Participation is completely voluntary, and patients will be informed of the usual process should they not care to be involved in this study.

10.0 Study Design / Methods

To complete Aims 1 through 3, we will conduct a single-center, 24-month, two-arm, semi-blind, 1:1 randomized controlled clinical trial involving 190 participants (95 in each arm), with roughly 55% (100 participants) being AA. The figure to the right outlines the study. The Aims of this study are to improve adherence and control of late clinical issues which are predominant



factors for racial disparities in kidney recipients, through a technology-enabled, telehealth-delivered 4-level intervention. The key clinical issues for this study include tac variability, BP, and glucose control (in those with DM). We will also assess the impact on the intervention on healthcare utilization (hospitalizations and ED visits) and conduct a cost-benefit analysis. Finally, we will assess the impact of the intervention on acute rejection and graft survival rates vs a large contemporary national cohort. The study design and intervention were developed using our formative research, providing insights into interventions that change behaviors, improve access, and address provider bias and structural racism, while being highly acceptable to patients.

To complete Aim 4, we will conduct a retrospective longitudinal cohort study, comparing a large contemporary national cohort of adult Veteran kidney recipients transplanted between 2015 and 2021 to our RCT intervention arm. We created a similar VA cohort, which we utilized to obtain foundational research supporting this proposal. Dr. Taber has a VA appointment and access to VA data.⁸ For this Aim, we will request an updated VA dataset linked to Medicare and USRDS, which includes recipient sociodemographics, donor information, transplant characteristics, labs, vital signs (BP, glucose, A1c, etc), medication refills, tac levels, acute rejection, hospitalizations, ED visits, and graft outcomes.⁸ Inclusion and exclusion criteria will match the RCT to obtain a similar study population. Only those with at least 2-years of graft survival will be included. Outcomes will be captured until graft loss/death or end of follow-up (Dec 2023). The national cohort will be divided by race and compared to the intervention arm from the RCT. We will measure tac variability, BP control and DM control, as well as acute rejection, graft loss, and death, comparing cohort data to RCT data.

11.0 Data Management

Data capture will be accomplished using electronic extraction, manual chart abstraction, and through direct patient interviews (when necessary) by a blinded study coordinator. The blinded coordinator will not have access to the randomization module in the electronic research database. Data will be collected by conducting a thorough review of the patient's medical records with patient phone calls when needed. Data collection will include all baseline donor/recipient demographics and transplant characteristics as well as medications, laboratory data, pathology, and clinical events which occur during the study. Data will also be captured through the web-based portal and linked to abstracted data within the research database. The Research Electronic Data Capture (REDCap) system will be used for data management. REDCap is a secure, web-based application designed exclusively to support data capture for research studies, which we have used in our previous clinical trials. REDCap provides: 1) an intuitive interface for data entry (with data validation); 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R); 4) procedures for importing data from external sources; and 5) advanced features, such as branching logic and calculated fields. Data for Aim 4 completion will be stored in the VA CDW research environment, VINCI.

Sample-size and power: This study is powered to detect clinically meaningful and statistically significant improvements in medication adherence (Aim 1), SBP control (Aim 2), DM control (Aim 2), and graft survival (Aim 4) while also demonstrating significant reductions in AA disparities for these endpoints (overarching Aim). The analyses take full advantage of all measurements captured during the entire 2-year study using repeated measure methodology. For tacrolimus variability (Aim 1), there will be 9 assessments (baseline and every 3 months), aligning with when labs are measured. Over the 2-year study, a 5% trajectory difference between arms for tacrolimus variability is considered clinically meaningful and is feasibly achievable given our pilot data (time*treatment).

Tac CV has an expected standard deviation of 8.5 with an approximate Gaussian distribution; thus, meeting normality assumptions. A sample size of 87 per group (n total=174) achieves >0.999 power, assuming both arms start with a tac CV of 35% and changing over the 2-year study to 32% in the control arm and to 27% in the treatment arm. The study is powered at 0.800 to specifically test for reductions in racial disparities between the intervention and control arms, using a 3-way interaction term in the model (time*treatment*race). For BP and glucose control (Aim 2), we will capture all home- and ambulatory-based measures aggregated into monthly assessments, totaling 25 (baseline and once monthly for 24 periods). We have 0.998 power to detect a difference in SBP changes between arms, assuming a mean SBP of 135 mmHg in both arms at baseline and a 5-mmHg reduction in the treatment arm, using 25 repeated measures (monthly). SBP has an expected standard deviation of 9.0 with a Gaussian distribution; thus, meeting normality assumptions. We have 0.800 power to test for reductions in racial disparities between the arms for SBP, using the time*treatment*race 3-way interaction term. We have 0.998 power to detect a difference between arms for glucose changes, assuming a mean baseline glucose of 160 mg/dL in both arms, 50% of patients having DM (N=87) at time of randomization and a trajectory difference in glucose of 24 mg/dL between arms (25 repeated measures).²⁰ We have 0.803 power to test for significant reductions in racial disparities between the two arms for glucose control, modeled using the time*treatment*race interaction term. Mean glucose has an expected standard deviation of 10.8 and distribution approximates Gaussian; thus, meeting normality assumptions. To account for dropouts and censoring events, we will increase each arm sample size to 95, totaling 190 participants. This is an inflation of approximately 10%, which is significantly above what is expected totals for dropouts (estimated to be between 2 to 3%), and power reductions due to censoring events.

For Aim 4, this study has adequate power to detect a statistically significant difference between the intervention arm and the national contemporary VA cohort for graft survival. Based on our previous research using the national VA database, we expect to identify roughly 8,500 kidney transplants from the VA transplanted between 2015 and 2021, representing a contemporary cohort (33% of which are expected to be AA). Annual graft loss attrition rates are expected to be 5% in the VA cohort (with a mean of 7-years follow-up time) and 3% in the RCT treatment arm (with 2-years follow-up time). Given these, we will have 0.780 power to detect a significant difference in graft survival between the VA national cohort and our intervention patients. To assess if the intervention reduced racial disparities in graft loss, we will compare the AAs in the RCT treatment arm to the roughly 2,800 AAs in the national VA cohort. We expect annual graft attrition rates to be 7% in the VA cohort (7-year mean follow-up) and 4% in the treatment arm (2-year follow-up). Given these estimates, we have 0.812 power to assess if the treatment intervention significantly reduced racial disparities for graft survival, as compared to the national contemporary VA cohort. These power analyses are valid across different data distribution assumptions (Gaussian, log-transformed). Power analyses were conducted using SAS 9.4 (SAS Proc GLMPower for Aims 1-2; SAS Proc Power; twosamplesurvival test=logrank for Aim 4; SAS Ins, Cary, NC).

Statistical Analysis Plan: We will use intent-to-treat principles; all randomized patients will be included in the analysis according to their allocated arm, even if they dropout, are lost to follow-up or have a censoring event.

Baseline Data and Comparisons: To assess for balance between arms, we will compare a comprehensive set of baseline recipient and donor variables, and transplant characteristics, using standard univariate tests (chi square, Fisher's exact test, t-test, Mann-Whitney U tests), as appropriate, based on data distributions and test assumptions. For the recipient, baseline variables will include age, sex, ESRD cause, dialysis type and vintage, comorbidities (diabetes, hypertension, CAD, CHF, etc), infection serologies (CMV, EBV, HSV, HCV, HBV), waitlist time, insurance

status, education level, disability, geographic location and social determinants of health measures, as specified by the NIH PhenX SDOH toolkit. For the donor, measures include age, sex, past medical history, infection serologies (CMV, EBV, HSV, HCV, HBV), and kidney donor risk index (KDRI). For the transplant characteristics, variables include time from transplant to enrollment, immunosuppression, HLA, PRA, cold ischemic time, warm time, and DGF. Variables that differ between arms will be analyzed as potential confounders in multivariable modeling, as described in the following sections below.

Primary and Secondary Outcomes: For the primary outcome (Aim 1, tac variability), repeated measures analyses will be conducted using generalized linear mixed modeling (GLMM). We will assess for tac CV distribution and use the appropriate link function and/or data transformation, if necessary, to ensure model assumptions are not violated. GLMM is the ideal model to use for this clinical trial as it provides robust estimates, takes full advantage of longitudinal data captured during the entire 2-year study, and accounts for a wide array of continuous data distribution types (e.g., Gaussian, log-normal, exponential, gamma) and discrete data distribution types for secondary outcomes (e.g., Poisson, binomial, and negative binomial). Assessments for tac variability will be made every 3 months, aligning with when labs are typically drawn. For treatment effect estimates, both unadjusted (raw) and multivariable adjusted modeling will be conducted in an iterative manner. The time*treatment interaction term will serve as the primary measure of efficacy, which estimates the longitudinal trajectory difference between arms over the entire 2-year study. A time*treatment*race 3-way interaction term will be used to assess for changes in racial disparities, as this term estimates if the longitudinal trajectory changes between arms differ by race. Statistical significance ($p < 0.05$) for this term indicates that the treatment effect significant differs by race (AA vs. non-AA). The direction of the estimate provides information regarding a reduction (negative value) or worsening (positive value) of the disparity. The magnitude of the estimate provides inferential quantification for the level of change in the disparity for that outcome. Additional measures of interest include change in the overall study population (time estimate) and the overall mean difference between arms (treatment estimate). TITR will be modeled in the same manner as tac CV. Models will be adjusted for key baseline covariates (age, sex, living donor, diabetes) and those that are not balanced at time of randomization (see above). In an iterative exploratory manner, we will also test for effect modification by age, sex, diabetes, and living donor status using interaction terms (e.g., treatment*age, treatment*sex, treatment*diabetes, treatment*living donor). If any of these interaction terms are significant, we will report findings in a stratified manner. For instance, if the treatment*sex interaction term is significant, we will report model parameter estimates separately for males and females. Depending on the distribution of the outcome, model estimates for the treatment will be reported as percent change or mean differences.

For secondary outcomes, which include BP and glucose (in those with diabetes), data will be aggregated into 25 repeated measure assessments (baseline and monthly for 2-year study). GLMM methodology will also be used for these outcome analyses. The primary efficacy measure for all secondary outcomes will be the time*treatment interaction term estimates (measure of difference in the slope between arms) from GLMM models. To specifically test for the impact of the intervention on racial disparities, the 3-way (time*treatment*race) interaction term will again be used, assessing the significance (p -value), the direction (negative or positive sign) and the magnitude in change (estimate level). For both the primary and secondary outcomes, graft loss and death will be considered censoring events, and analyses will include patient data accrued up until these events occurred. To assess for differences in infection rates by treatment arm and race, Poisson or negative binomial modeling will be conducted. Model estimates for rate ratios and 95% CI will be reported. Acute rejection, graft loss and death will be reported using Kaplan-Meier survival curves and compared using the Log Rank test. Multivariable modelling will be used to adjust for confounders,

using frailty Cox regression analysis. Hazard ratios and 95% confidence intervals will be reported. We will use alternative models depending on whether the proportional hazard assumptions for the Cox model is satisfied or not.¹¹⁶ The proportional hazards assumption is tested using Schoenfeld residual plots, log(-log) plots, and ASSESS PH in SAS.¹¹⁷ This procedure includes the treatment arm as fixed-effect and is known to produce a precise, robust inference. To test for the impact of the intervention on racial disparities for graft outcomes and death, a 2-way (treatment*race) interaction term will be entered into these Cox models.^{116,117}

Healthcare Utilization and Cost-Benefit Analysis (CBA): Healthcare utilization will be estimated by measuring the number of hospitalizations, length of stay, and ED visits that occur in patients during the 2-year study and comparing these between study arms (Poisson or negative binomial modeling). Total hospital charges will be analyzed using two-part statistical models for zero-heavy continuous data. The general format of the model is that we fit a logistic model for the probability of non-zero response and a conditional generalized linear model (GLM) for the mean response given that it is non-zero. We will consider several distributions for the GLM part (log-normal, gamma, and Weibull) and the best fitting model will be selected using Bayesian Information Criterion (BIC). Parameter estimates of percent change in total charges per unit increase in the values of each covariate in the model and 95% CI will be computed using SAS Proc FMM. This procedure allows estimating regression coefficients and to conduct hypothesis testing on the mean difference in the costs between arms, and to identify factors that are associated with total charges among those with non-zero values.¹¹⁸⁻¹²⁰ For a comprehensive CBA, we will also conduct an ROI analysis.³¹ All costs associated with the delivery of the intervention will be recorded during the conduct of the study, including pharmacist time needed to deliver the intervention, other personnel effort costs, fees paid to refine and maintain the app and dashboard system, and costs to buy and ship supplies to patients.³¹ To convert hospitalization charges to costs, the Medicare cost report will be used, and charges will be multiplied by the SC Medicare mean cost-to-charges ratio (CCR) for 2022 through 2027, which currently is 0.27.¹²¹ All charge data will be converted to 2027 dollars using healthcare inflation rates published by the Consumer Price Index.¹²² The total cost savings from expected reductions in hospitalizations and ED visits (based on our R18 RCT) will be subtracted from intervention costs; a positive value indicates a positive ROI (absolute net savings).

Schedule of Measurements and Assessments:

Measurement or Assessment	Baseline	M2	M3	M4	M6	M8	M9	M10	M12	M14	M15	M16	M18	M20	M21	M22	End of Study
Demographics, PMH, Transplant Characteristics, Donor Info	X																
Tacrolimus CV, TITR	X		X		X		X		X		X		X		X		X
SrCr, Ur Pr/Cr Ratio, DSA, DD cfDNA, Clinic BPs, eGFR*	X	O^	O^	O^	O^	O^	O^	O^	O^	O^	O^	O^	O^	O^	O^	O^	O^
IMAB Q10 Adherence Survey	X		X		X		X		X		X		X		X		X
Home BP Measurements and Adherence	X		X		X		X		X		X		X		X		X
Home Glucose Measurements and Adherence**	X		X		X		X		X		X		X		X		X
Immunosuppression Regimen and Doses		X		X	X	X		X	X	X		X	X	X		X	X
Hospitalizations, LOS, and Cause		X		X	X	X		X	X	X		X	X	X		X	X
ED Visits and Cause		X		X	X	X		X	X	X		X	X	X		X	X
Kidney Biopsies, Acute Rejection, and Treatment		X		X	X	X		X	X	X		X	X	X		X	X
Infections and Treatment		X		X	X	X		X	X	X		X	X	X		X	X
Graft Loss and Cause																	X
Death and Cause***		X***															

X: required; O: optional

*When available from usual care measurements, ^Only when measured as part of standard of care, **Only in those with diabetes, ***As soon as study team becomes aware

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

The data safety monitoring plan will include the use of a safety officer and the MUSC IRB to monitor the study-related safety, clinical outcomes, and potential adverse events (AEs). Any reportable events and safety concerns will be reported to the MUSC IRB by the PI, as soon as they become aware of it. Additionally, the DSMP will utilize the study statistician to review the data generated by the MITIGAAT study and ensure data integrity and assess potential for futility. Summaries of AE reports and safety concerns raised by the safety officer will be made to the NIH in yearly progress reports unless the nature of a particular event is such that it bears reporting to the NIH immediately. The designated safety officer for the MITIGAAT study is a well-experienced transplant physician who is not directly involved in the intervention component of the study. The designated statistician responsible for data oversight and creating the reports needed for the DSMP meetings is an experienced biostatistician with knowledge in monitoring clinical research data integrity. Both the safety officer and the biostatistician will coordinate data review and analysis and communicate with the study PI and the co-investigators. The functions of the designated safety officer are to: 1) provide scientific oversight; 2) review all serious adverse effects or complications related to the study; 3) monitor accrual; 4) review summary reports relating to compliance with protocol requirements; and 5) provide advice on resource allocation.

The safety officer and statistician will meet at the following four pre-designated study milestones: each time 95 participants have received at least 12-months of study follow-up care (two meetings) for the RCT, once 95 participants have completed the RCT (one meeting), and shortly after the final participant, final visit. The team will also meet on an as needed basis for any unexpected serious adverse events or significant study findings. Data will be provided at these meetings by the biostatistician on key variables that may indicate harm, including hospitalizations, graft loss and death. Study participant clinical events, including acute rejections and life-threatening infections,

will also be reviewed during these sessions. The biostatistician will evaluate confidentiality and integrity of the database, and the procedures for recording and storing confidential files. The safety officer will also review the elements of the research plan to deal with emergencies. At the conclusion of these meetings, the recommendations of the safety officer will be reviewed and the PI and co-investigators will take appropriate corrective actions as needed.

The safety officer will have the authority to halt the trial if he/she perceives that harm is occurring due to the interventions.

Institutional IRB: The IRB will review and approve the protocol, review consent forms, ensure protection of patient privacy and safety, and monitor the study on an ongoing basis. Study-related severe adverse events will be reported to the IRB as they occur. Annual reports to the IRB will indicate accrual rate, adverse events, new findings that may influence continuation of the study, and significant findings of the safety officer.

13.0 Withdrawal of Subjects

Participation in this study is completely voluntary. Participants may withdraw at any time during the study. Treating physicians or providers may also request participants are withdrawn from the study if there are any safety concerns with participation. Participants that withdraw will be asked if they are willing to allow the data already collected on them to be included in analyses. Inclusion in the data analysis is also completely voluntary. If participants are agreeable, patient data will be censored at the time of withdrawal and these patients will be included in the intent-to-treat analyses.

14.0 Risks to Subjects

Potential Risks: This study will not involve requiring patients to take any experimental medications or medications that are not approved by the FDA. All patients, regardless of randomization, will receive standard usual care that is provided by MUSC to all kidney transplant recipients. Any adjustments or changes made to the patient's medication regimen in the intervention group will be approved by the transplant physicians involved in this study as co-investigators, either a transplant surgeon or transplant nephrologist, depending on the intervention. There will be increased monitoring and scrutiny of participants' home blood pressures, glucoses, laboratories, medication regimens and adherence to medication, monitoring and appointments (those in the intervention arm). However, based on our experiences with two previous clinical trials that employ a similar intervention, we do not anticipate this increased scrutiny to lead to deleterious outcomes or stress on intervention group participants, but we will monitor for this through our data safety monitoring plan, and should an issue arise, the safety officer has the authority to temporarily halt or permanently stop the study.

Although it is expected that MITIGAAT will improve clinical surrogate markers and outcomes, it may also increase stress on patients and increase the potential of identifying false positive information. We will minimize the risk of this causing harm to study patients by ensuring all data is closely monitored by a highly trained transplant clinician. All interventions made based on this study will be reviewed and approved by a transplant physician, similar to what occurs during usual care processes.

Randomization: Whether a patient is in the intervention group, or the control will be by random selection using a random number generator, in blocks of ten.

Unknown Risks: The researchers will inform patients if they learn anything that may alter patient's views about participating in the study. Since all patients in both arms of this study are receiving standard of care, no additional risks are foreseen with this study.

Adequacy of Protection Against Risks

Protection against Risk: There should not be any extensive risks to patient safety during the completion of this study: no investigational medications will be used and all changes to patient's current medication regimens will be made in accordance with and under the direct approval of a transplant physician. In order to protect subjects against any risk regarding loss of personal information, all obligations under the Health Portability and Accountability Act (HIPPA) will be met. Additionally, all data will be collected and stored through the secure network server and behind the MUSC firewall. We will use electronic CRF forms approved by the IRB to gather all study information. Data will only be stored on campus computers under the MUSC secure network. Data collection forms will be maintained within an office, which is a locked office facility on campus. Only approved study members will have access to patient data.

Any data or information shared for dissemination will be de-identified and the confidentiality of all participants will be strictly maintained. The only persons with access to protected health information (PHI) will include study investigators, research coordinators and those approved by the MUSC IRB. All data will be secured on MUSC servers, behind firewalls, with passwords protecting entry in these systems. All PHI will be obtained and managed in accordance with the HIPAA Privacy Rule (45 CFR Parts 160 and 164).

Increased scrutiny and remote monitoring using technology and a clinical pharmacist may lead to an increased awareness and documentation of laboratory values and non-adherence. However, we expect these to be identified and managed very early in their course before they can induce harm to the patient requiring further health care interventions. Early and efficient identification of medication non-adherence and control of common comorbidities (hypertension, diabetes and anemia) are the primary factors that we expect to be the mediator of the signal for improved graft survival within the intervention arm. To ensure this is occurring in a safe manner, the DSMP will include detailed monitoring of clinical outcomes, including acute rejection episodes, graft loss and graft function. If there are signals that the intervention is actually inducing higher rates of these incidents, then the designated safety officer, an experienced transplant physician, has the authority to stop enrollment and/or close the study (see the DSMP). We fully expect clinical outcomes and surrogate markers to improve in the intervention arm, as compared to the control arm. We do, however, have a comprehensive plan to address issues if this is, in fact, not the case.

15.0 Potential Benefits to Subjects or Others

Patients in the intervention group may have improved management of medication therapy and comorbidities, resulting in improved clinical surrogate markers. This may potentially lead to a signal of improved graft survival in the intervention arm. Regardless, the completion of this study will produce data that will lead to a better understanding of the incidence, timing and true causes of medication adherence issues and suboptimal control of comorbidities in long-term kidney transplant

recipients. Even if the intervention is not successful in its objectives, this information can be utilized to design and test different intervention strategies to reduce these clinical markers. It is hoped that the information gained from the study will help the researchers learn more the incidence, timing and true causes of medication adherence issues and suboptimal control of comorbidities in long-term kidney transplant recipients and determine if a multimodal, mHealth, telehealth delivered intervention can improve the efficient monitoring and effective management of this complex patient population.

16.0 Sharing of Results with Subjects

Results will be shared with participants after the study is complete. We will share results by updating the clinicaltrials.gov website with outcomes data and sharing the site with patients enrolled in the study. We will also share results to healthcare providers through presentation at transplant conferences and publication in peer reviewed journals.

17.0 Drugs or Devices

This is a health services intervention, and as such, is not testing a drug or particular therapy. Rather, the intervention is testing the use of innovative technology to improve the efficient and effective delivery of care. The mobile health app used in this capacity is not used to diagnose or cure and is considered excluded software by the FDA. This is not considered a medical device.

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