IMPROVING TRANSPLANT MEDICATION SAFETY THROUGH A PHARMACIST-EMPOWERED, PATIENT-CENTERED, MHEALTH-BASED INTERVENTION

(TRANSAFE Rx Study)

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A Introduction

A1 Study Abstract

Although the contemporary use of immunosuppression regimens have dramatically reduced the incidence of acute rejection, long-term graft survival continues to be suboptimal in kidney transplantation. Studies suggest that adverse drug events and medication errors, both of which encompass medication safety issues, may be a predominant cause of graft loss. However, despite kidney transplant recipients being at high-risk for medication safety events, there is limited information surrounding the incidence, etiologies and outcomes of medication (med) errors and adverse drug events within this population. Our preliminary research has demonstrated that significant medication errors, predominantly due to patient-related factors, occur in nearly two-thirds of kidney transplant recipients, leading to hospitalization in one out of every eight patients. Recipients that develop clinically significant med errors are at considerably higher risk of deleterious clinical outcomes, most significantly graft loss; these patients also develop substantially more adverse drug events, readmissions and acute rejections. Researchers have also demonstrated feasibility and high acceptability of mobile health (mHealth) technology use to bridge communication gaps that often lead to med safety issues. Smartphone and home-based monitoring technology has a very high penetration rate within this population. These studies establish that a pharmacist-empowered, patient-centered, mHealth-based intervention provides an innovative and highly promising opportunity to improve med safety in kidney transplantation. It is within this context that the Improving Transplant Medication Safety through a Pharmacist-Empowered, Patient-Centered, mHealth-Based Intervention (TRANSAFE Rx) study was developed. The primary goal of the TRANSAFE Rx study is to demonstrate significant reductions in med safety issues leading to reduced healthcare resource utilization in kidney transplantation through a pharmacist-led, mHealth-enabled, intervention. This study will provide detailed and novel information on the incidence, etiologies and outcomes of med errors and adverse drug events in this high-risk population; while also demonstrating the effectiveness of this intervention on reducing the incidence and impact of med safety issues in kidney transplantation. The enduring goals of this study are to demonstrate a highly effective, efficient and deployable method to improve medication safety in high risk patient populations with the long-term objective of disseminating this promising technology and intervention across multiple patient types and healthcare environments.

A2 Primary Hypothesis

Hypothesis 1: Patients in the intervention arm will have significantly fewer med errors and adverse drug events, as compared to the usual care arm, at the end of the 12-month study

Hypothesis 2: The intervention arm will have significantly fewer healthcare encounters (clinic visits, ED visits and hospitalizations), leading to reduced costs, as compared to the usual care arm, at the end of the 12-month study

A3 Purpose of the Study Protocol

Due to the complexities and toxicities associated with their immunosuppressive medication regimens, kidney transplant recipients are at high-risk of developing medication safety issues which can lead to hospitalization, increased healthcare expenditures and ultimately, graft loss. Founded on preliminary information, the use of pharmacists and mHealth technology provide a promising and innovative approach to

improve medication safety in high-risk patients. The ultimate goal of this research is to demonstrate how patients, pharmacists and technology can work hand-in-hand to optimize medication-related outcomes and reduce healthcare expenditures.

B Background

B1 Prior Literature and Studies

Within kidney transplantation, despite dramatic improvements in acute rejection rates, long-term graft survival has not improved to nearly the same degree. Since 2003, there has been a 50% reduction in acute rejection rates; yet, during this same time period, the kidney allograft half-life has only increased by a modest 0.6 years.(3, 4) The most recent report from the Scientific Registry of Transplant Recipients (SRTR) demonstrates a historically low one-year acute rejection rate of <10%, with a suboptimal five-year graft survival rate of 70%.(1) Medication safety issues, which encompass both medication errors and adverse drug events, are a predominant cause of deleterious clinical outcomes in kidney transplant recipients; most notably, graft loss.

We, and others, have demonstrated that approximately two-thirds of transplant recipients will experience at least one medication error. (8-10) Of more concern, nearly one in eight kidney transplant recipients will experience a medication error which directly contributes to hospitalization and more than doubles the risk of graft loss (Figure 1). These medication errors are usually the result of unintentional medication non-adherence (MNA); patients have difficulty obtaining medications or forgetting to take medications in a timely fashion.(11) MNA, usually due to unintentional patient-level factors, has now been recognized as a major contributor to late acute antibody mediated rejection (AMR), the development of donor specific antibodies (DSA) and subsequent graft loss. In a prospective multicenter observational study, 315 kidney transplant recipients were followed for roughly three years post-transplant; 47% of the 50 allografts that failed during follow-up were due to AMR. Thirty-two percent of patients were identified as having MNA and approximately one-half of all AMRs were due to MNA. Remarkably, MNA was 10 times more frequent in patients with graft failure (32% vs. 3%, p<0.001).(23) As most MNA is unintentional, with the proper monitoring tools and clinical follow-up, this devastating risk factor appears to be modifiable.

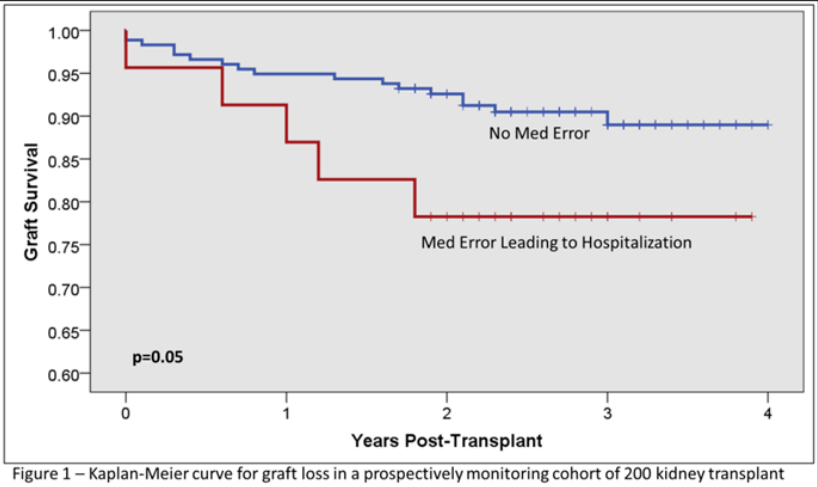


Figure 1 – Kaplan-Meier curve for graft loss in a prospectively monitoring cohort of 200 kidney transplant recipients, comparing those that developed a medication error leading to hospitalization versus control patients.

Although contemporary immunosuppression is extremely effective at preventing rejection, adverse drug events are nearly universal and associated with significant post-transplant morbidity. Several studies suggest that adverse drug events, particularly surrounding infection from over-immunosuppression and calcineurin inhibitor nephrotoxicity, may be a predominant cause for the discordance noted between reductions in acute rejection and lack of improvements in graft survival. In 2006, Parasuraman, et al. showed that infectious etiologies surpassed rejections as the leading cause of death-censored graft lost.(6) Our formative research demonstrates that immunosuppressant adverse drug events are correlated with medication errors; patients that experience medication errors leading to hospitalization have 2.3 times the risk of developing at least three adverse drug events (p=0.020, Table 1).(11) In other chronic disease states, adverse drug events have clearly been established as a major risk factor for MNA.(24-27) Therefore, early recognition of adverse drug events in kidney transplant recipients will likely help prevent downstream clinical sequelae, including MNA and irreversible immunosuppressant toxicities. Research demonstrates that clinical pharmacists have the unique education and training to identify these events early, while also developing strategies to mitigate or resolve the associated sequelae.(13, 14, 28-32)

Table 1 – Clinical and economic outcomes based on developing a clinically significant med error

Outcome	Clinically Significant Med Error (n=23)	No Medication Error (n=177)	p-Value
LOS of Post-Transplant Readmissions (median, IQR)	5.0 (2.0 – 14.0)	0.0 (0.0 – 5.5)	<0.01
Costs of Post-Transplant Readmissions (median, IQR)	$18,091 ($3K- $56K)	$0 ($0 - $16K)	<0.01
Adverse Drug Reactions* - None	4%	15%	0.172
At Least One	96%	85%	0.172
At Least Two	70%	51%	0.091
At Least Three	35%	15%	0.020
At Least Four	9%	5%	0.475

The impact of kidney allograft loss on clinical and economic outcomes cannot be overstated. Annual death rates are more than three times higher in those with kidney allograft failure (9.4%), compared to those with a functioning transplant (2.8%).(33) A well-functioning kidney allograft has also been shown to dramatically reduce the progression of cardiovascular disease and associated events.(28-30) In terms of cost, kidney transplantation is clearly cost-effective. However, due to high and varied peri-operative costs associated with this surgery, the break-even point can range from 2 to 11 years after transplant.(31, 32) Once a kidney allograft fails, patients return to dialysis and costs to provide care accrue at a significantly higher rate.(33, 34) Our research indicates that kidney transplant recipients that experience clinically significant medication errors spend five more days in the hospital for readmissions, costing more than $18,000 per case.(11) These data establish the need for innovative interventions designed to improve medication safety in kidney transplant recipients by reducing medication errors and adverse drug events;(7) Such medication safety improvements are needed to demonstrate significant progression in the optimization of long-term graft outcomes and patient survival, while considerably reducing the costs to provide high value care in this high-risk group of patients. Control of chronic health conditions, exacerbated by immunosuppressive therapies, also has a major impact on allograft and patient survival.(34,35) Due to the high prevalence of hypertension and diabetes in kidney transplant recipients and the interplay between these diseases and graft outcomes, this

is an ideal population to test mHealth systems and their effects on outcomes for future application in a more widespread population.

B2 Rationale for this Study

Kidney transplantation is considered the preferred treatment option for patients with end-stage renal disease, with more than 140,000 patients living in the U.S. with a functioning transplant. The use of potent contemporary immunosuppression has significantly decreased acute rejection rates, with current one year rates of <10%, compared to 30 to 40% three decades prior.(1-3) Despite this, long-term renal allograft survival remains largely unchanged during this time period. Studies have demonstrated that predominant causes of graft loss are driven by immunosuppression adverse drug events (patient harm related to a med) and rejection from med non-adherence.(4-6) These origins of graft loss encompass issues directly related to med safety. Current immunosuppression regimens are highly effective but carry the burdens of considerable toxicities and exceeding complexity.(7) These attributes place a transplant patient at high risk of developing adverse drug events and med errors. Despite this, there are limited studies analyzing the incidence, etiologies and outcomes associated with med safety issues.(8, 9) Our formative research has demonstrated that med errors (taking a med in a manner not intended), predominantly due to patient-related factors, occur in nearly two-thirds of kidney transplant recipients, leading to hospitalization in one out of every eight recipients.(10,11) We have also found that recipients that develop clinically significant med errors are at considerably higher risk of deleterious clinical outcomes, most significantly graft loss; these patients also develop substantially more adverse drug events, readmissions and acute rejections.(10,11)

Our team has published non-controlled quality improvement initiatives demonstrating reduced med errors, adverse drug events, hospital length of stay and readmissions through pharmacist-led interventions.(12-15) These studies provide foundational evidence that structured interventions can improve outcomes associated with med safety issues in transplant, but further data are required both to better understand contributing risk and etiologies, while also testing effectiveness of novel interventions in a prospective, controlled manner. We have demonstrated feasibility and high acceptability of mobile health (mHealth) technology to bridge communication gaps that often lead to med safety issues. Our transplant recipients have doubled smartphone use to over 60% from 2012 to 2015.(16-18) Almost 90% of survey respondents indicated they were comfortable with mHealth monitoring and felt it improve timely patient-provider communication.(17) Transplant recipients were central to successful development of a mHealth medical regimen self-management program which the proposed program builds upon.(16,19) These data establish that a pharmacist-empowered, patient-centered, mHealth-based intervention provides an innovative and promising opportunity to improve med safety in kidney transplantation. Our mHealth programs and that of others have been successful in improving physical markers for various chronic diseases, including those present in transplant recipients (e.g. BP for hypertension); however cost-effectiveness of these efforts have yet to be adequately demonstrated. (16, 19-22)

The central hypothesis for the TRANSAFE Rx study is that a mHealth technology-enabled pharmacist intervention will significantly reduce med safety issues and lead to reduced healthcare resource utilization in kidney transplantation.
This study will provide novel data on the incidence and outcomes of med safety issues in transplantation, while demonstrating the effectiveness of a pharmacist-led, patient-centered, mHealth intervention. The enduring goals of this study are to demonstrate a

highly effective, efficient and deployable method to improve med safety in a high-risk patient population and disseminate this mHealth enabled program across multiple patient types and healthcare environments.

C Study Objectives

C1 Primary Aim

- Determine the incidence, severity and etiologies of med errors and adverse drug events in kidney transplant recipients and compare these between the intervention and control cohorts.

C2 Secondary Aims

- Measure the total resources utilized (hospital, outpatient, staff effort) to provide care and compare these between the intervention and control cohorts.

- Measure the impact of med errors and adverse drug events on clinical outcomes, including acute rejections, infections, graft loss and death (exploratory aim)

D Study Design

D1 Overview or Design Summary

TRANSAFE Rx is a 12-month, parallel two-arm, 1:1 randomized controlled clinical trial, involving 136 participants (68 in each arm) and measuring the clinical and economic effectiveness of a pharmacist-led intervention, which utilizes an innovative mHealth application to improve medication safety and health outcomes, as compared to usual post-transplant care. The planned study design and interventions of this project were developed from the aforementioned foundational studies. These preliminary studies provided insight into interventions that were clinically effective, efficiently implementable, had a high-rate of patient acceptability and were capable of being scalable to a wide-array of patient populations. It is within this framework that the investigators have designed the TRANSAFE Rx study.

D2 Subject Selection and Withdrawal

2.a Inclusion Criteria

1) Kidney transplant recipient between 6 and 36 months post-transplant
2) At least 18 years of age
3) Transplant MD agrees that patient is eligible to participate

2.b Exclusion Criteria

1) Multi-organ recipient
2) Patient is incapable of:
    a. Measuring their own blood pressure
    b. Measuring their own glucose (if subject has diabetes)
    c. Self-administering medications
    d. Speaking, hearing and reading English
    e. Utilizing the mHealth application, after training

2.c Ethical Considerations

Ethical considerations for randomized, controlled trials include informed consent, risk of harm by the intervention, and risk of loss of confidentiality. Subjects eligible for this study will undergo an informed consent process with a study coordinator that is trained in the process and has completed the Collaborative IRB Training Intiative (CITI) offered online by the University of Miami. The PI of the study will be available for any questions and the subject will be provided adequate time to make an informed decision, as described in section 2(c). Because the intervention is technological, the greatest additional risk to the subjects is loss of confidentiality. Only data that is necessary for the purpose of the study will be collected. Subject data will only be available on password-protected devices and only encrypted data will be transferred.

Protection of Human Subjects: MUSC researchers are allowed the privilege of working with human subjects under normal assurance to the government that such research complies with regulations protecting human subjects. The university has a federal-wide assurance for research with human subjects and is in compliance with federal policy governing use of human subjects. Investigators involved in human subject research at MUSC are required to complete the Collaborative IRB Training Initiative (CITI) offered on line by the University of Miami. In addition, all human subject protocols are reviewed through the MUSC Institutional Review Board (IRB). The Office of Research Integrity coordinates the activities of three IRB committees, involving faculty members as well as representatives in the legal, ethical, religious, civic, and business communities.

Compliance: The MUSC University Compliance Program is a proactive program to ensure full agreement with all applicable policies, procedures, laws and regulations. This involves a confidential Compliance Helpline to encourage all members of the MUSC community to ask questions or voice concerns about laws and regulations on such topics as coding and billing, research integrity, professional ethics, human subjects, animal research, biological safety, conflict of interests, and patient confidentiality. The program office proactively trains employees and facilitates discovery of concerns, followed by appropriate investigation into problem areas and timely resolution of issues. This program directly assists MUSC's management at all levels in maintaining and enhancing an environment where ethics are paramount considerations in strategic and operational decisions throughout the organization.

2.d Subject Recruitment Plans and Consent Process

Subject Identification/Recruitment:
Adult (≥18 years old at the time of transplant) solitary kidney transplant recipients 6 to 36 months post-transplant that meet study eligibility will identified through review of patients visiting the kidney transplant clinic as part of usual care and approached by research personnel for consideration for participation.

Informed Consent:
Authorized research personnel will approach patients to explain the study and offer the opportunity to participate in the study. The personnel who will obtain consent will have completed Human Subjects Protection Training. This research study will be explained in

lay terms to each potential research participant. In compliance with the informed consent process outlined in CFR Title 21 Part 50, the authorized personnel will conduct a face-to-face meeting with the study candidate to review all of the required elements of informed consent. The potential study participant will sign an informed consent form before undergoing any screening study procedures. The original consent form will be kept with the subject's file in the office. A copy of the consent will be given to the patient and another copy will be put in his/her chart. At the time of consent, patients will be assured that their care will not be affected in any way if they choose not to participate in the study. Patients will also be reminded that it is their right to withdraw their participation in the study at any time.

2.e Randomization Method and Blinding

Randomization Method:
Whether a patient is in the intervention group or the control will be by random selection using a random number generator in a simple blocked manner (blocks of 8).

Blinding:
This is an open-label study, so subjects and the research team will be aware of the study assignment. Due to the nature of the intervention, blinding of the subject and research staff is unable to be performed. In order to minimize bias, data for outcomes will be collected by a blinded study coordinator.

2.f Risks and Benefits

There are minimal risks to patient safety during the completion of this study within the intervention arm and no risks with regards to study interventions within the control arm. This study will not involve requiring patients to take any experimental medications. All patients, regardless of randomization will receive standard usual care as part of this study. Any adjustments or changes made to the patient's medication regimen in the intervention group will be approved by a transplant physician. There will be increased monitoring and scrutiny of patient's home blood pressures, glucoses and medication regimens. All documented medication errors and adverse drug events will be identified by a blinded research coordinator at the same frequency and methodology across intervention and control patients. This will minimize the likelihood of identifying higher rates of medication safety issues in the intervention group. The risk associated with the intervention arm is in loss of patient confidentiality, which will be mitigated through the use of HIPPA compliant data encryption on mobile devices and storage of PHI on password protected databases behind the MUSC firewall.

Although it is expected that this will improve medication safety, 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 clinical pharmacist. All interventions made based on this will be reviewed and approved by a transplant physician.

The study research coordinator will identify medications errors and adverse drug events within both arms, but clinicians will not be privy to this information as part of usual care. However, usual care and follow up will ensure all patients in both arms receive the most up to date and effective care that is provided in the current health care environment. Should these identified, but not acted upon, medication safety issues induce patient

harm, it will be closely tracked by the research personnel and reported as detailed in the DSMP. Through this plan, we are minimizing all potential risks for patients participating in this study.

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

Recruitment and Informed Consent

Participation in the study will be voluntary. Patients who have received a renal transplant 6 to 36 months post-transplant will be identified during routine clinic visits for usual care. Subjects who meet inclusion criteria for the study will be asked about their desire to participate. Patients will be required to complete an informed consent document to ensure they understand the goals, risks, and potential benefits of the study before any research related activities occur.

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 Information Portability and Accountability Act (HIPAA) 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 medication side effects and adverse drug events. 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 identification and resolution of medication errors, side effects and adverse drug events is the primary factor that we expect to be the mediator of reduced health care encounters and costs. To ensure this is occurring in a safe manner, the DSMP will include detailed monitoring of health care encounters and clinical outcomes, including acute rejection episodes 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 (section E3.a). We fully expect these event rates to reduce 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.

Potential Benefits of the Proposed Research to the Subjects and Others

Patients in the intervention group may have reduced incidence and burdens associated with medication safety issues. This may potentially lead to reduced health care associated encounters, visits to the clinic and/or hospital and costs. Regardless, the completion of this study will produce data that will lead to a better understanding of the incidence, severity, root cause and potential outcomes associated with medication safety issues within kidney transplant recipients. This information can be utilized to design and test different intervention strategies to reduce these events, should the proposed intervention within this study fail to demonstrate meaningful results.

Importance of the Knowledge to be Gained

It is hoped that the information gained from the study will help the researchers learn more about the incidence, severity, root cause and potential outcomes associated with medication safety issues within kidney transplant recipients and determine if a pharmacist-led mHealth enabled intervention can potential reduce these events.

2.g Early Withdrawal of Subjects

If a study subject desires to prematurely terminate the study intervention, if possible, a visit will be scheduled with the Principal-Investigator (PI) or designee within seven days to evaluate the reason for early termination. It will be clarified whether they are terminating from all components of the trial or only from the primary intervention component of the trial. Ultimately, subjects have the autonomy to withdraw from the study or stop the intervention if they so desire.

2.h When and How to Withdraw Subjects

Subjects will complete the study at the end of the 12-month follow up period or at the time they wish to prematurely terminate the study.

2.i Data Collection and Follow-up for Withdrawn Subjects

If a study subject wishes to terminate the study intervention, but are willing to continue to report outcomes, they will have outcome data collected until their final study visit. If any subject wishes to terminate from all aspects of the study and withdraw, data collection will cease from that point on and outcomes will be censored at that point for data analysis.

D3 Study Intervention

3.a Treatment Regimen

Intervention Cohort

Patients randomized to the intervention cohort will be provided the same usual care as the control cohort. In addition, this cohort of participants will receive clinical pharmacist-led supplemental medication therapy monitoring and management, utilizing a smartphone-enabled mHealth application, integrated with televisits and home-based monitoring of blood pressures and glucoses (when applicable). Subjects in this cohort will be provided with a mobile device/data plan if they are not current owners of an iPhone. All will also be provided with a Bluetooth-enabled, automated, cuff-style bicep home blood pressure monitor and a Bluetooth-enabled digital home blood glucose monitor. On the mobile device, a HIPPA compliant app developed by our collaborative group will be installed that displays the patient's medication list and alerts them when it is time to take each medication, requiring them to indicate if the medication was taken for adherence tracking. Through the app, medication regimen-specific symptom surveys will be pushed to patients that ask the frequency and severity of common side effects of their medications. The intervention will include a clinical transplant pharmacist telemonitoring patient medication adherence and blood pressure/glucose readings (if applicable) weekly and scheduling telehealth visits with patients, as outlined in Table 2.

Table 2 – Televisit schedule based on patient risk and events

Risk Level	Definition	Scheduled Televisits	Triggered Televisits
High	Meets 2 or more of the following High-Risk Criteria • <80% adherence to medications • Missed clinic visits • Blood pressure outside of 20% of goal • <80% of blood sugars within goal range • Moderate to severe side effects	Twice Monthly	• Patient reported medication change or initiation • New severe medication side effect • Critical home values of blood pressures or glucoses • Any transition in care
Moderate	• Meets 1 of the High-Risk Criteria	Monthly	
Low	• Does not meet any of the High-Risk Criteria	None Necessary	

The clinical transplant pharmacist will be alerted by the patient if there are medication changes made by outside providers, by way of making adjustments to the medication regimen in the mobile app. At this point, the patient will be contacted to evaluate the medication change and determine if the adjustment to the regimen is safe and effective. If the pharmacist deems this change to be of concern, they will work with the patient and transplant physician to alter the regimen in an appropriate manner. In addition, the pharmacist will be alerted if the patient has evidence of significant nonadherence (≥20% missed self-reported medication doses in the course of a week), if they have blood pressure or glucose values that fall into critical ranges or if there are alarming trends in their readings or symptom assessments from surveys. Upon receiving these alerts, the pharmacist will communicate with the patient, determine the root cause and coordinate care with other care providers as delineated at the bottom of Figure 4.

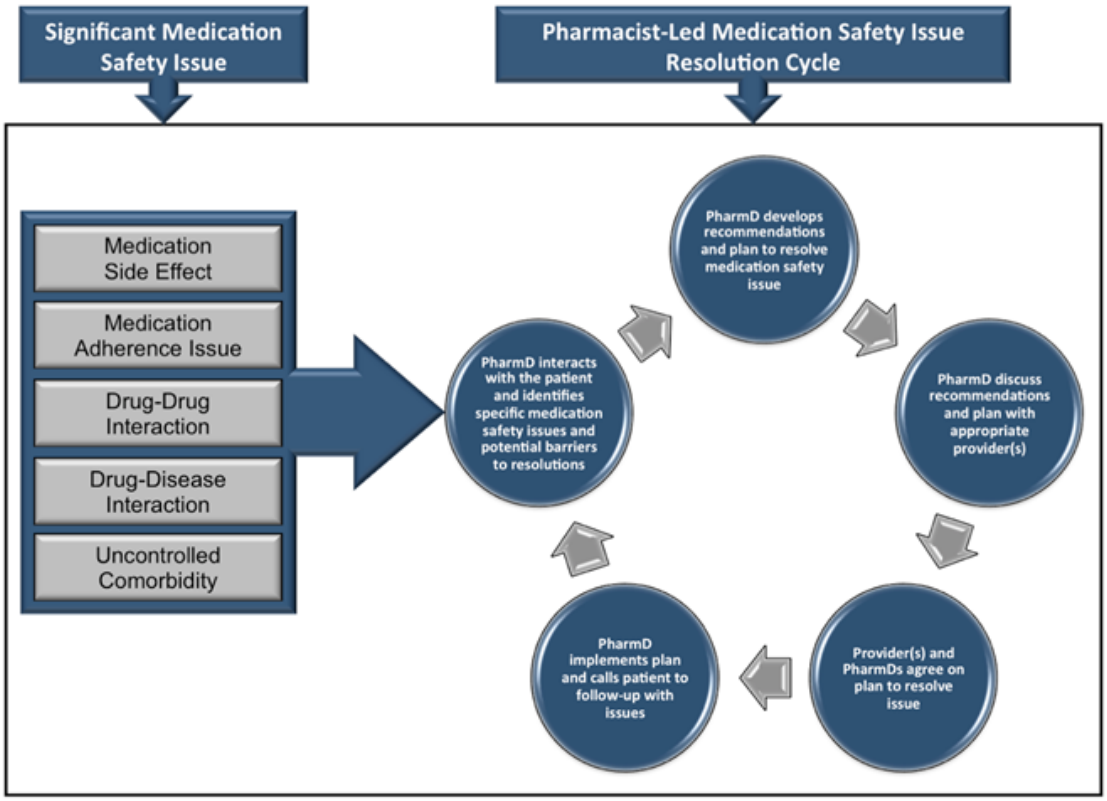


Figure 4 – Cycle describing the process used by pharmacist to resolve medication safety issues

During televisit encounters, the transplant pharmacist will conduct a thorough medication review, evaluate for signs and symptoms suggestive of medication safety issues, screen for drug-drug and drug-disease interactions and provide recommendations to resolve identified issues to the patient and/or provider, when applicable. The clinical pharmacist will be alerted and evaluate each patient when making a transition of care (inpatient admission or discharge) to ensure accurate medication regimens are communicated to accepting teams and to the patient. The same ambulatory EPIC note template that is used by the clinical pharmacist during the usual care visits will be utilized for documentation during these telehealth encounters. EPIC is the inpatient and ambulatory EHR utilized within the study institution. The process used to resolve medication safety issues during distant monitoring is outlined in Figure 4. Once the clinical pharmacist identifies an issue, they will develop a management plan using the algorithm detailed in Figure 5, discuss the recommendations with the providers, agree on a plan, and implement the plan with direct patient follow-up. The algorithm in Figure 5 encompasses the major medication safety issues, including side effects, adherence, drug interactions and less than optimally controlled comorbid disease states.

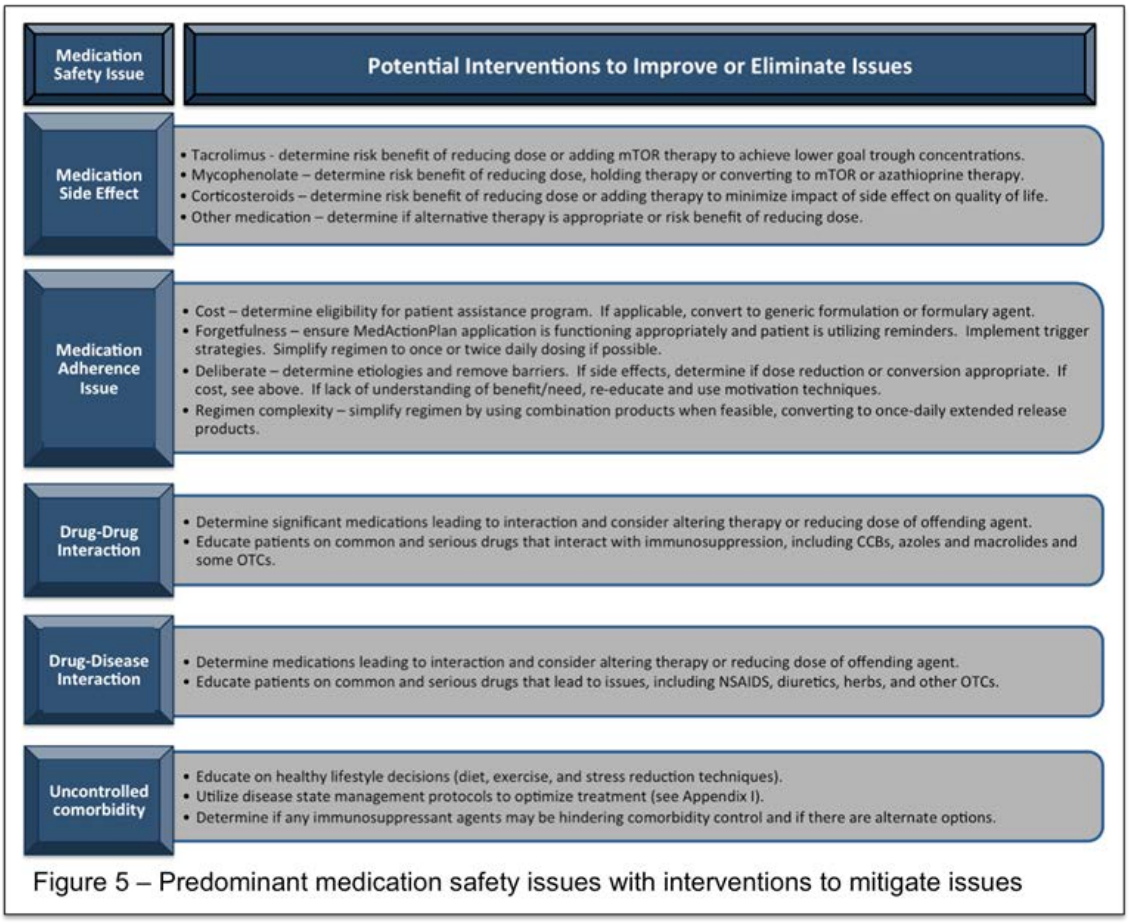


Figure 5 – Predominant medication safety issues with interventions to mitigate issues

This algorithm is a guideline, and the transplant pharmacist will use this, as well as their clinical judgment and professional experience, to develop the medication safety issue resolution plan.

mHealth Medication Safety Monitoring and Management Tool: Patients in the intervention cohort will have enhanced medication safety monitoring utilizing an integrated mHealth system, coalescing the EHR (EPIC) with an application developed by our research collaborative and FORACare telehealth systems to provide a seamless, bidirectional, patient-centered, home-based monitoring tool that will allow for early, effective and efficient identification of medication safety issues by the clinical transplant pharmacists. The application will provide patients a useful tool to conduct self-care monitoring and management, including timely reminders to take medications, automated messages when patients miss multiple medication doses, tracking of medication side effects and reporting trends in blood pressures and glucoses (when applicable). Using our foundational research and through previous collaborations, we have partnered with Technology Applications Center for Healthful Lifestyles (TACHL) to incorporate monitoring tools and patient questionnaires that will minimize intrusions, while maximizing the potential of identifying medication safety issues, including medication errors, nonadherence and adverse drug events, early in their course. Figure 6 lays out the conceptual diagram of this system, detailing how it will allow for the efficient creation and reconciliation of accurate medication regimens, while also monitoring medication

adherence and signs and symptoms of potential medication safety issues (medication errors or adverse drug events).

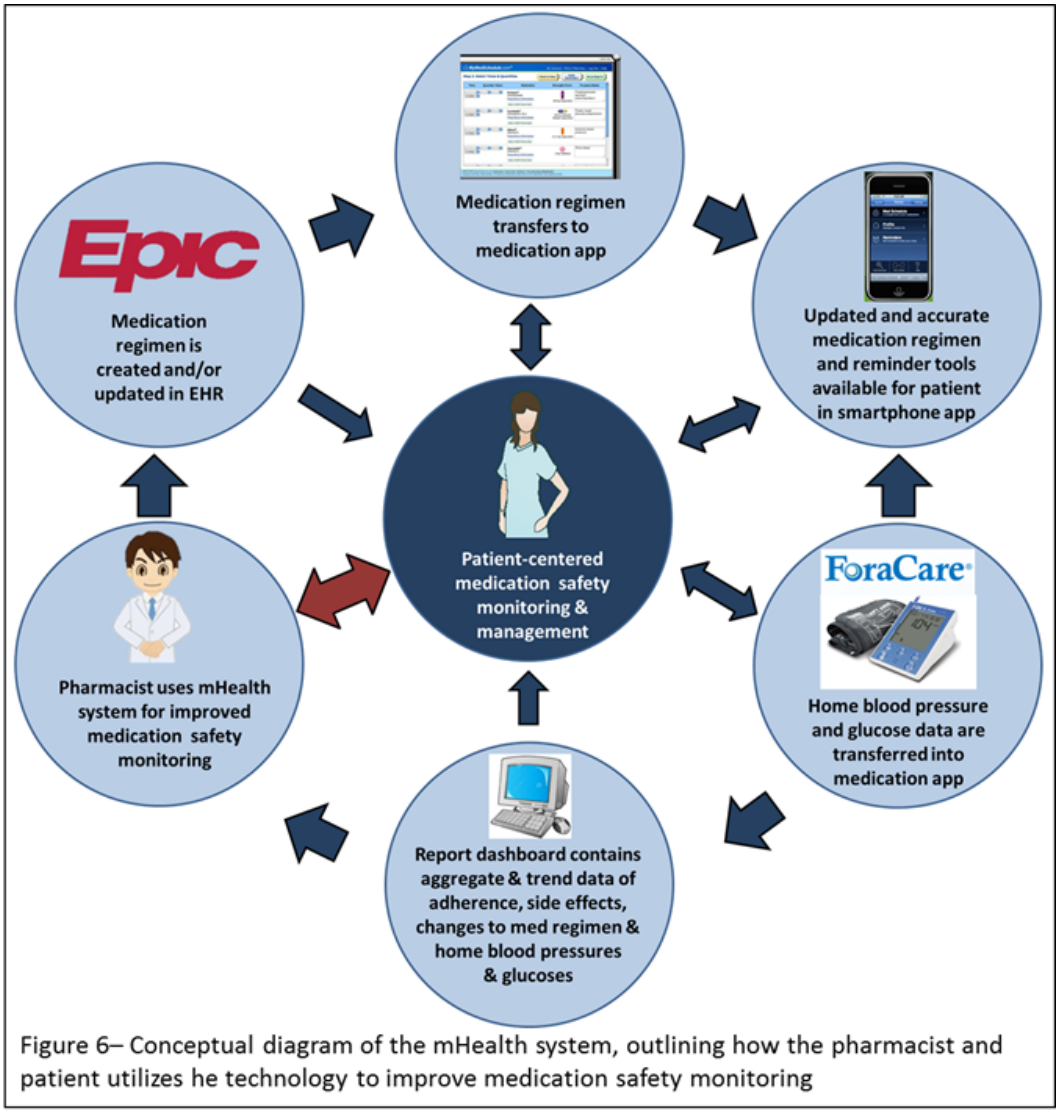


Figure 6– Conceptual diagram of the mHealth system, outlining how the pharmacist and patient utilizes he technology to improve medication safety monitoring

Starting in the top left corner of Figure 6, the medication regimen is created or updated in the EHR by the transplant pharmacist or other qualified healthcare professional. This data flows into the medication app (top middle of figure), through a continuity of care document (CCD), which contains machine-readable patient information. The app accepts CCDs via direct messaging (government sponsored encrypted email), SFTP and FTPS. Upon receipt, the app parses the CCD and uses its data to create a patient friendly medicine schedule, where it is then updated and verified for accuracy by the transplant pharmacist. Once verified, the medication regimen flows into the patient's mobile smartphone device (top right of figure). Each medicine will include its purpose, route of administration, special instructions (e.g., "Avoid grapefruit and grapefruit juice"), possible side effects and adherence record. The smartphone application allows the patient to have an accurate, updated list of their medication regimen, while also providing reminders to take medications at the correct times. Medication reminders will include a checkbox for each medication. The patient will be asked to check the box if

they have taken that medicine. These self-reported responses get tabulated and recorded in the program as an adherence score for that medicine and an overall score for all medicines. As part of this study, the clinical pharmacist will have access to this data in the report dashboard, located on a secure HIPAA compliant website. If the patient changes or updates their medication regimen through the application, an email will be sent to the transplant pharmacist, who will contact the patient to determine the medication, dose and interval and review it as outlined in Figure 4. Once all issues are resolved, the pharmacist will enter the medication into the EHR as a self-reported medication.

Home-based monitoring of blood pressures and glucoses, using the FORACare system, will also transfer into the application and the report dashboard.(42, 43) The app will also give providers the ability to create and send surveys to the patient. The survey will populate on the patients' home screen as an alert message. The alert message will not disappear until the survey has been filled out and submitted. Survey responses get recorded in the app and are incorporated into the report dashboard. As part of this study, patients in the intervention cohort will receive medication side effect surveys during gaps in transplant clinic visits. The survey was developed using the validated Memphis Medication Side Effect Survey, coupled with our formative research demonstrating which side effects are associated with the adverse drug events that are most commonly associated with hospital readmission.(44-46) Patients will complete this survey and this data will then flow into the report dashboard for review as aggregate and trend information. Thus, this mHealth system will allow both the patient and transplant pharmacist to track signs and symptoms of medication safety issues.

3.b Method for Assigning Subjects to Treatment Groups

Whether a patient is in the intervention group or the control will be by random selection using a random number generator in simple blocks of 8.

3.c Subject Compliance Monitoring

Monitoring for compliance with medications, clinic visits, blood pressure and glucose monitoring (if applicable) is a part of the intervention in the intervention cohort. If subjects are not complying with data monitoring in the intervention cohort, they will be contacted by the study pharmacist to encourage use of the smartphone and any relevant Bluetooth-enabled devices. If this does not resolve the noncompliance, the subject will be contacted by the study PI to discuss continued involvement in the study.
These data will not be monitored real-time in the usual care cohort. Compliance with study data capture will be monitored by the study coordinators, who are completely independent of the pharmacists providing the interventions. They will gather data via direct subject interview and through review of the subject's electronic medical records.

3.d Blinding of Study Intervention

This is an open-label study, so subjects and the research team will be aware of the study assignment. Due to the nature of the intervention, blinding of the subject and research staff is unable to be performed. In order to minimize bias, data for outcomes will be collected by blinded study personnel, as much as feasibly possible.

E Study Procedures

E1 Screening for Eligibility

Adult (≥18 years old at the time of transplant) solitary kidney transplant recipients 6 to 36 months post-transplant that meet study eligibility will be approached by research personnel for consideration for participation at the time of a usual care clinic visit or healthcare encounter with the transplant team.

E2 Schedule of Measurements

All patients in both arms of the study will continue to receive usual post-transplant care. The supplemental care that is provided to the intervention group will all be via remote monitoring and televisits, also detailed in section above. In addition, there will be two study specific clinic visits and four televisits that occur in all patients (both control and intervention arms), as detailed in the table below. The Baseline visit will not be counted as a study visit, as this will be the usual care visit patients are identified, screened, consented and randomized at. The table below outlines these visits and what will be assessed during the visits.

Assessment	Base-line	Month 2	Month 4	Month 6	Month 8	Month 10	Month 12
Obtain informed consent, collect baseline patient and transplant information	X						
Assessment for medication errors				X			X
Tele assessment for medication errors		X	X		X	X	
Assessment for adverse drug events				X			X
Tele assessment for adverse drug events		X	X		X	X	
Assessment for health care encounters				X			X
Tele assessment for adverse health care encounters		X	X		X	X	
Chart review assessment for acute rejection(s)	X	X	X	X	X	X	X
Chart review assessment for infection(s)	X	X	X	X	X	X	X
Chart review assessment for graft function, graft loss and death	X	X	X	X	X	X	X

E3 Safety and Adverse Events

3.a Safety and Compliance Monitoring

The data safety monitoring plan (DSMP) includes the use of a safety officer, with overarching IRB oversight, to monitor the study-related clinical outcomes, medication side effects, and adverse events. Additionally, the DSMP will utilize the study statistician to review the data generated by the TRANSAFE Rx study and ensure data integrity. Summaries of adverse event reports and patient 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 TRANSAFE Rx 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 work closely with the study PI and the co-investigators. The functions of the designated safety officer are to: 1) provide scientific oversight; 2) review all 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 seven pre-designated study milestones: each time 34 patients have received at least six months of study follow-up care (four meetings), once 68 patients have completed the study (one meeting), once 102 patients have completed the study (one meeting), and at study close-out. 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 investigators on key variables that may indicate harm, including significant medication safety events leading to hospitalization or intervention. Study patient clinical events, including hospitalizations, emergency room visits, acute rejections, life-threatening infections, graft loss and patient death 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.

3.b Medical Monitoring

i Investigator only

Investigators will monitor for serious adverse events and report them as indicated in the sections above. Additionally, adverse drug events and medication errors will be tracked as a study endpoint, with interim results reported as detailed in the DSMP.

ii Independent expert to monitor

The designated safety officer for the TRANSAFE Rx study is a well-experienced transplant physician who is not directly involved in the intervention component of the study. The functions of the designated safety officer are to: 1) provide scientific oversight; 2) review all 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 will have the authority to halt the trial if he/she perceives that harm is occurring due to the interventions.

iii Institutional Data and Safety Monitoring Board

The IRB will review and approve this clinical research protocol and patient consent forms, as well as have oversight for 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, if they were unexpected and deemed to be related to the study intervention. Annual reports to the IRB will indicate accrual rate, adverse events, new findings that may influence continuation of the study, and reports provided as part of the DSMP.

iv Independent Data and Safety Monitoring Board

The DSMP will review the data generated by the TRANSAFE Rx study. Summaries of adverse event reports and any patient safety concerns raised by the safety officer will be made to the NIH/IRB in yearly progress reports unless the nature of a particular event is such that it bears reporting to the NIH/IRB immediately. The designated statistician responsible for data oversight and creating the reports needed for the DSMP meetings will be 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 work closely with the study PI and the co-investigators The safety officer and statistician will meet at the following seven pre-designated study milestones: each time 34 patients have received at least six months of study follow-up care (four meetings), once 68 patients have completed the study (one meeting), once 102 patients have completed the study (one meeting), and at study close-out. 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 investigators on key variables that may indicate harm, including significant medication safety events leading to hospitalization or intervention. Study patient clinical events, including hospitalizations, emergency room visits, acute rejections, life-threatening infections, CV events, graft loss and patient death 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.

3.c Definitions of Serious Adverse Events and Adverse Drug Events

Serious adverse events (SAEs) for this study are defined as hospitalizations, acute allograft rejections, graft losses and deaths that are unexpected and deemed to be directly related to the study intervention, as determined by the PI and reviewed during oversight in the DSMP reports. All SAEs will be reported to the IRB as they occur.

Adverse drug events (ADEs) will be defined according to the AHRQ Patient Safety Network, in which it describes an adverse drug event as "an adverse event (i.e., injury resulting from medical care) involving medication use.(21) The severity of the adverse drug event will be defined according to a modified version 4.0 of the CTCAE developed by the National Cancer Institute. The CTCAE is a standardized classification system developed to assess the frequency and severity of adverse events. It was originally designed for cancer patients, but is now routinely utilized across multiple patient types in clinical research.(48, 49) The modified CTCAE utilized by the study investigators for this study can be found at the end of this document. ADEs will be summarized in DSMP reports and categorized by severity and study arm. These reports will be provided to the IRB on an annual basis.

3.d Classification of Events

Adverse drug events will be classified according to the modified CTCAE, as detailed above.

3.e Data Collection Procedures for Serious Adverse Events and Adverse Drug Events

In both the usual care and intervention arms, a highly trained clinical research coordinator will independently interview all participants at bimonthly intervals to capture and record all medication errors and adverse drug events, including timing, likely cause and severity of each event. These events will be further reviewed and adjudicated by a pharmacist not involved in delivering the study intervention, in a blinded fashion. To assess for medication errors, the research coordinator will review and compare the patient's documented medication regimen in the electronic health record (the regimen intended to be taken) to the medication regimen actually being taken by the patient, which will be assessed using the patient's medication bottles and/or lists.

Serious adverse events will be continuously screened for by chart review for new hospitalizations, kidney biopsies, and deaths. The EHR will be utilized, as it has alerting systems capable of screening and notifying the study coordinator and PI of events within study patients.

To assess for adverse drug events, the research coordinator will review patient symptomology, vital signs and laboratory values. The research coordinator will be trained by the study pharmacists in identifying medication errors and adverse drug events, determining causality and grading the severity. To ensure objectivity and consistency in recording these events across both study cohorts, a number of safeguards will be instituted. First, the study investigators will utilize the same research coordinator to record all medication errors and adverse drug events. Second, this research coordinator will be completely independent of the telehealth intervention that is being performed and will be blinded to the patient's randomized group. Third, only the medication errors and adverse drug events recorded by this research coordinator will be

used for data analysis. Finally, these patient assessments will be followed by an independent assessment by a clinical transplant pharmacist that is not associated with delivering the study intervention. This will ensure that event rates are not biased towards a higher capture rate in the intervention cohort, which will be receiving more intense scrutiny of their medication regimens by a clinical pharmacist.

E4 Study Outcome Measurements and Ascertainment

The primary outcome measure of this study will be the incidence and severity of medication errors and adverse drug events, which will be identified, categorized and compared between the intervention and control cohorts as detailed above and in the following sections. The exploratory outcome measures of this study are to compare the incidence and severity of acute rejections, infections, graft function, graft loss and death between research cohorts and measure the association between medication safety issues and these events. Demonstrating improvements in acute rejections, infections, graft loss or death within the intervention group will provide the data needed to design a larger, multicenter study (through dissemination efforts detailed at the end of this proposal). Additional data that will be gathered includes patient surveys to capture measures of sociodemographics, health literacy, depression, social support and trust. These are important variables that may modify or confound the impact of the intervention.

Study endpoint definitions and assessment plan:
The following will be used to define and capture data and events within this study:

1. Medication errors will be defined as documentation that a patient is taking a medication in a manner that was not intended; synonymous with the definition developed by Overhage and utilized within our previous research.(11,14).

2. Adverse drug events will be defined according to the AHRQ Patient Safety Network, in which it describes an adverse drug event as “an adverse event (i.e., injury resulting from medical care) involving medication use”.(21) The severity of the adverse drug event will be defined according to a modified version of the CTCAE developed by the National Cancer Institute and utilized in our previous research. The CTCAE is a standardized classification system developed to assess the frequency and severity of adverse events. It was originally designed for cancer patients, but is now routinely utilized across multiple patient types in clinical research.(48, 49). In both the usual care and intervention arms, a highly trained clinical research coordinator will independently interview all participants at bimonthly intervals and review their medical records to capture and record all medication errors and adverse drug events, including timing, likely cause and severity of each event. To assess for medication errors, the research coordinator will review and compare the patient’s documented medication regimen in the electronic health record (the regimen intended to be taken) to the medication regimen actually being taken by the patient, which will be assessed using the patient’s medication bottles. To assess for adverse drug events, the research coordinator will review patient symptomology, vital signs and laboratory values. Prior to the study being opened for enrollment, the research coordinator will be extensively trained by the study pharmacists in identifying medication errors and adverse drug events, determining causality and grading the severity.

3. Acute rejection will be defined as a renal allograft biopsy demonstrating at least grade 1A rejection by Banff '97 criteria or higher or treated borderline rejection.(50) All patients will be required to have biopsy confirmation of rejection episodes within 24 hours of onset of treatment for acute rejection, as per our protocol and usual. 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 the local pathologist, as usual care. This pathologist will not be informed of participant participation in the study and will be blinded to cohort assignment. The study coordinator capturing clinical event data, different from the coordinator capturing medication error and adverse drug event data (to ensure blinding is maintained), will review the medical record at regular intervals to determine the incidence, timing, severity, treatment regimen and reversibility of each acute rejection episode for all study participants.

4. Infections will be defined as any diagnosed and treated infection, and will be sub-classified as bacterial, viral, or fungal etiologies. Flu-like illnesses and viral syndromes NOT requiring antimicrobial therapy will not be defined as infections for this study. Opportunistic infections will also be sub-classified for this study as viral, bacterial or fungal and defined as infections not seen in immunocompetent individuals; the most common opportunistic infections in kidney transplant recipients include CMV, BK, EBV and candidiasis.(51, 52) The study coordinator capturing clinical event data, different from the coordinator capturing medication error and adverse drug event data (to ensure independence is maintained), will review the medical record at regular intervals to determine the incidence, timing, severity, treatment regimen and cure timing of each infection episode for all study participants.

5. Graft function will be defined using the 4-variable MDRD equation to estimate GFR. This equation has been validated as an accurate reflection of true GFR within kidney transplant recipients.(53) Routine serum creatinine concentrations, which are measured as part of usual care, will be utilized to estimate GFR at these *approximate* time points: baseline, 3, 6 and 12 months post-enrollment.

6. Graft failure will be defined as return to chronic dialysis, transplant nephrectomy, retransplantation or death. The study coordinator capturing clinical event data, different from the coordinator capturing medication error and adverse drug event data (to ensure independence is maintained), will review the medical record at regular intervals to determine if a study patient has developed graft failure. The timing and cause of each graft loss will be recorded for comparative analysis. Patient death will also be captured in a similar fashion, with timing and cause recorded as well.

7. Healthcare encounters will be defined as any direct encounter (face-to-face) between the study patient and a physician or advance practice provider (APP) occurring within a licensed healthcare facility and occurring during the 12-month study. These encounters will be categorized as ambulatory clinic visits, ambulatory procedure visits, acute care/emergency room visits and hospitalizations. Hospitalizations will be defined as an admission to a hospital with at least one overnight stay. Length of stay within the hospital for readmissions will also be captured. Healthcare encounters will be captured through direct study subject interviews with patients at bimonthly intervals.(36) The study coordinator will record all healthcare encounters that have occurred. If the patient has a health care encounter outside of the study institution, the research coordinator will document the type of encounter to estimate costs, as detailed below.

8. Costs associated with care will be assessed based on data from hospital accounting at the study institution, once the study is completed. Costs will be measured from the time of randomization up until the end of the 12-month follow-up period. Analyses will include all costs associated with inpatient and outpatient care, including hospitalizations, ambulatory care visits, ambulatory procedure visits, acute care/emergency room visits and laboratory assessments. Costs uniquely associated with the intervention group will include the costs of the devices and data plan provided to the patients, time necessary for training patients on use of the technology and research pharmacist time associated with the intervention. Total costs will be calculated for each cohort. These data will be electronically captured by providing a list of patient's MRNs to hospital accounting after the completion of the study to allow for accurate and complete billing information to accrue. Costs associated with healthcare encounters that occur outside the study institution will be estimated by acquiring information from the patient regarding the type of encounter and using this data to estimate cost based on cost/charge ratios from the study institution. This will be a costs - consequences analysis (CCA)] using cost effectiveness methodology, taken from the societal perspective.

F Statistical Plan

F1 Sample Size Determination and Power

Based on previous studies conducted by our research collaborative, we estimate that approximately 64% of kidney transplant recipients in the control group will experience a medication error during the one year study (defined using the Overhage criteria).(1, 2) Our previous research demonstrates that pharmacist-led initiatives can reduce these medication errors by approximately 50%.(3, 4) Using these estimates, enrolling 104 participants (52 in each cohort), will provide 92% power in detecting a statistically significant difference in medication error event rates, with a two-tailed α=0.05. We will also have 94% power (two-tailed, α=0.05) to detect a 33% reduction in significant adverse drug events (CTCAE grade 3 or higher), given an estimated incidence rate of 87% in the control cohort and the strong association between medication errors and adverse drug events.(2, 5) From previous analyses, we expect that the control cohort will have a mean of 18.4±2.6 healthcare encounters (clinic visits, acute care/ER visits and hospitalizations), during the one year study. We estimate the intervention group will see an 8% absolute reduction in total encounters, to a mean 17.0 encounters, with an estimated 33% relative reduction in the mean number of hospital readmissions (1.2 vs. 0.8, respectively).(2) Given these estimates (two-tailed, α=0.05), enrolling 52 patients in each arm will provide 80% power to detect a statistically significant difference. It is estimated that the intervention will also produce a mean cost savings of at least $2,489 per patient ($7,658 in the control cohort and $5,169 in the intervention cohort, with σ estimated at $4,530).(2) This study is expected to have >80% power to detect a statistically significant difference in total post-transplant costs between cohorts, given these estimates.

For the exploratory outcomes of acute rejection, infections, graft function, graft loss and death, this study is not powered to detect statistically significant differences in these clinical events between groups. However, we expect to demonstrate meaningful clinical signals, particularly with a reduction in acute rejection. Our previous study demonstrated an acute rejection rate that was 1.8 times higher in patients experiencing a significant medication error (13.7% vs. 7.7%, respectively).(2) Thus, we expect an overall acute rejection rate of 12% in the control cohort and 9% in the intervention cohort,

corresponding with a 25% relative reduction in acute rejection rates. Based on previous randomized controlled trials conducted within the study institution, we expect to maintain an 85% retention rate.(6) We will adjust our total sample-size to 136 patients (68 in each cohort) to account for dropouts, thus maintaining adequate sample-size to produce at least 80% power to detect statistically significant differences in the primary outcome measures.

F2 Interim Monitoring and Early Stopping

The safety officer and statistician will meet at the following seven pre-designated study milestones: each time 34 patients have received at least six months of study follow-up care (four meetings), once 68 patients have completed the study (one meeting), once 102 patients have completed the study (one meeting), and at study close-out. 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 investigators on key variables that may indicate harm, including significant medication safety events leading to hospitalization. Study patient clinical events, including hospitalizations, emergency room visits, acute rejections, life-threatening infections, graft loss and patient death 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.

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

F3 Analysis Plan

This analysis will incorporate the intent-to-treat principle, namely, all randomized participants will be included in the analysis according to their intervention assigned at baseline. The two groups will be compared using standard statistical analyses. Data will be reported using percentages for nominal and ordinal variables and compared using Fisher's exact test or Pearson's chi-squared test as appropriate. This includes baseline demographic and transplant characteristic variables, as well as the outcome variables of the incidence and severity of medication errors and adverse drug events, acute rejection and infections. For continuous variables with normal distribution, results will be reported using means and standard deviations with statistical comparison using Student's t-test for two independent samples. For *non-normally distributed* variables, the results will be reported using medians and interquartile ranges, with statistical comparison conducted using the Mann Whitney U test. Normal distribution of continuous variables will be assessed using normality plots and the Shapiro-Wilk test. Normal variance will be assessed using Levene's test for equality of variances. Results for graft and patient survival will also be reported using Kaplan-Meier survival curves and compared using the Log Rank test.

If it is determined that there are significant imbalances in baseline demographics or characteristics known to influence any of the outcome measures, multivariable modelling will be used to adjust for these differences. For nominal outcomes, binary logistic regression will be used in a standard entry fashion, which will include both the grouping variable and all known risk-factors. For continuous outcomes that demonstrate linearity

in the relationship between dependent and independent variables, with a lack of serial correlation between covariates, homoscedasticity of the errors and normality of the error distribution, linear regression will be utilized in a similar manner. We will adjust for baseline values if the interventions are discrepant at baseline. This model will include the intervention arm and baseline response as fixed-effects and is known to lead to very precise inference.(7) If any of the four aforementioned assumptions are violated, then the data variables will either be transformed or appropriate substitute multivariable modelling will be used. Cox proportional hazard regression analysis will be used for time-dependent survival analyses involving the outcomes of graft and patient survival. For count outcomes, such as health care encounters, we will use Poisson regression; if the assumption of equal mean and variance is violated (over dispersion), we will use Negative Binomial regression. In all models, we will adjust for correlation of outcomes by including random effect terms. For all models that belong to the generalized linear model (linear, logistic, Poisson), we will use generalized estimating equations (GEE), and for survival outcomes, we will use frailty Cox regression.(8) We will use multiple imputation techniques to deal with missing data that is at random (MAR).(9) MAR assumes that the probability that an outcome is missing depends on observed outcomes. While mechanisms for missingness are likely to be MAR, we will also do sensitivity analysis for data missing not at random (MNAR) using methods from Little and Rubin.(9)

F4 Statistical Methods

The two groups will be compared using standard statistical analyses. Data will be reported using percentages for nominal and ordinal variables and compared using Fisher's exact test or Pearson's chi-squared test as appropriate. This includes baseline demographic and transplant characteristic variables, as well as the outcome variables of the incidence and severity of medication errors and adverse drug events, acute rejection and infections. For continuous variables with normal distribution, results will be reported using means and standard deviations with statistical comparison using Student's t-test for two independent samples. For *non-normally distributed* variables, the results will be reported using medians and interquartile ranges, with statistical comparison conducted using the Mann Whitney U test. Normal distribution of continuous variables will be assessed using normality plots and the Shapiro-Wilk test. Normal variance will be assessed using Levene's test for equality of variances. Results for graft and patient survival will also be reported using Kaplan-Meier survival curves and compared using the Log Rank test.

F5 Missing Outcome Data

We will use multiple imputation techniques to deal with missing data that is at random (MAR).(9) MAR assumes that the probability that an outcome is missing depends on observed outcomes. While mechanisms for missingness are likely to be MAR, we will also do sensitivity analysis for data missing not at random (MNAR) using methods from Little and Rubin.(9)

F6 Unblinding Procedures

No unblinding procedures are necessary, as this is as open-label study.

G Data Handling and Record Keeping

G1 Confidentiality and Security

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 to gather all study information (redcap.musc.edu). 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).

G2 Training

The intervention pharmacists will participate in a thorough training session with the TACHL group and PI. During this training, the dashboard's functionality will be reviewed, along with the standard operating procedure manual which fully guides interventions. Pivotal sessions that occur during this conference will include: review of dashboard specifics, alert functions using the dashboard, assessing clinical relevance of alerts, alert categories, interventions to address alerts, clinical and research documentation, and provider collaboration mechanisms. The investigational team will lead these sessions to deliver the presentations.

Research coordinators will also be thoroughly trained by the investigational team on assessing and documenting medication errors, adverse drug events and clinical outcomes. Detailed algorithms will be provided to the study coordinators to assist with these assessments and documentation, to ensure study fidelity. In addition, the pharmacist conducting the adjudication of these events will also be trained to ensure that the assessments and documentation of events are consistent across all individuals.

Before the study is opened for recruitment, a site initiation visit (SIV) will occur whereby all transplant clinical personnel will be invited and the study specifics will be presented. This, along with regular emails to the transplant group, will ensure that the study is well understood by both clinical and research personnel prior to initiation.

H Study Administration

H1 Organization and Participating Centers

The Medical University of South Carolina will be the only participating center.

H2 Funding Source and Conflicts of Interest

The study is funded by AHRQ. None of the investigators have any conflicts of interest related to this study.

H3 Committees

There is one group formed specifically for the conduct of this study, which is the DSMC. The DSMC will consist of the PI, co-investigators, study coordinator, statistician, data manager and consultants on the proposal. The functions of the DSMC will include: 1) providing scientific oversight; 2) reviewing all serious adverse events (adverse drug events, graft loss and death events, compared across intervention groups) or complications related to the study; 3) monitoring site adherence to the intervention; 4) reviewing summary reports relating to compliance with research protocol requirements; and 5) providing advice on resource allocation. The DSMC will meet according to the safety monitoring plan (Section 4.b.iv) and as necessary by telephone or in person. The recommendations of the DSMC will be reviewed and the PI will take appropriate corrective actions as needed. The intervention clinical pharmacists group will include the clinical pharmacists that were assigned to the intervention arm of the study. During the study, this group will have monthly meetings to discuss the intervention, identify and resolve study related issues and discuss pertinent study-related materials.

H4 Subject Stipends or Payments

Patients will be paid $50 for each study visit, not including the baseline visit, which will occur during a usual care visit. Thus, if patients complete the 12-month study, they will be remunerated $100 total, which is provided to cover travel and parking costs associated with the study visits.

H5 Study Timetable

The target dates for major milestones are detailed below. We expect to complete this trial and present final results within 36 months, based on the following:

- IRB submission: Target of July 31, 2017
- IRB approval: Target of August 31, 2017
- Technology development and testing complete: Target of September 30, 2017
- Study Open for Recruitment: Target of October 15, 2017
- Expected Enrollment by June 30, 2018: Target of 68 patients enrolled
- Last Patient Enrolled: Target of March 31, 2019
- Expected Enrollment by June 30, 2019: Target of all 136 patients enrolled, with 68 completed the study
- Last Patient, Last Visit: Target of March 31, 2020
- Complete Data Analysis: Target of April 30, 2020
- Begin to Make Technology Available to Other Pharmacists Managing Non-Transplant Patients: Target of Spring 2020
- Present Final Results at National Meeting (American Transplant Congress, ACCP): Target of May and June 2020
- Present Results to AST Transplant Pharmacy COP: Target of June 2020
- Complete Final Write-Up and Manuscript Submissions: Target of June 30, 2020

I Publication Plan

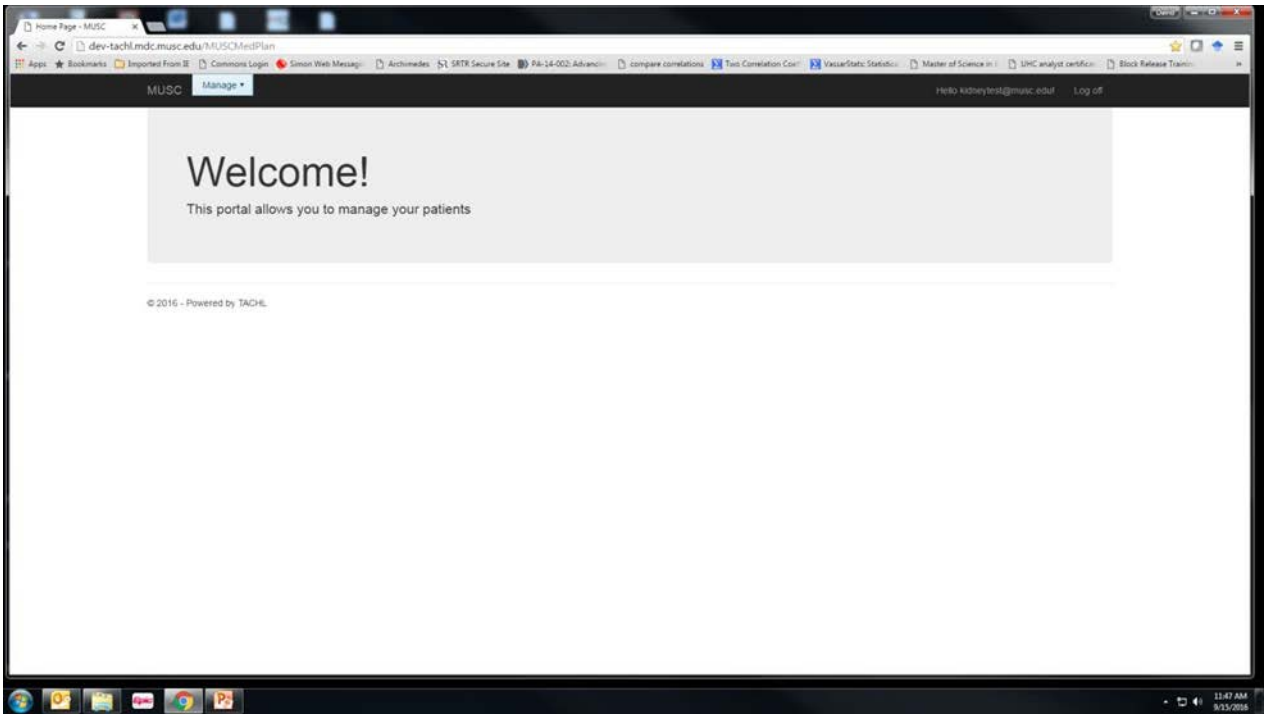
Planned publications include submissions to the following potential journals:

1) American Journal of Transplantation
2) Drug Safety
3) Health Technology Assessment
4) Journal of Medical Internet Research
5) American Journal of Kidney Diseases
6) Journal of the American Society of Nephrology
7) Clinical Journal of the American Society of Nephrology
8) Kidney International
9) Journal of the American Medical Association
10) Annals of Internal Medicine

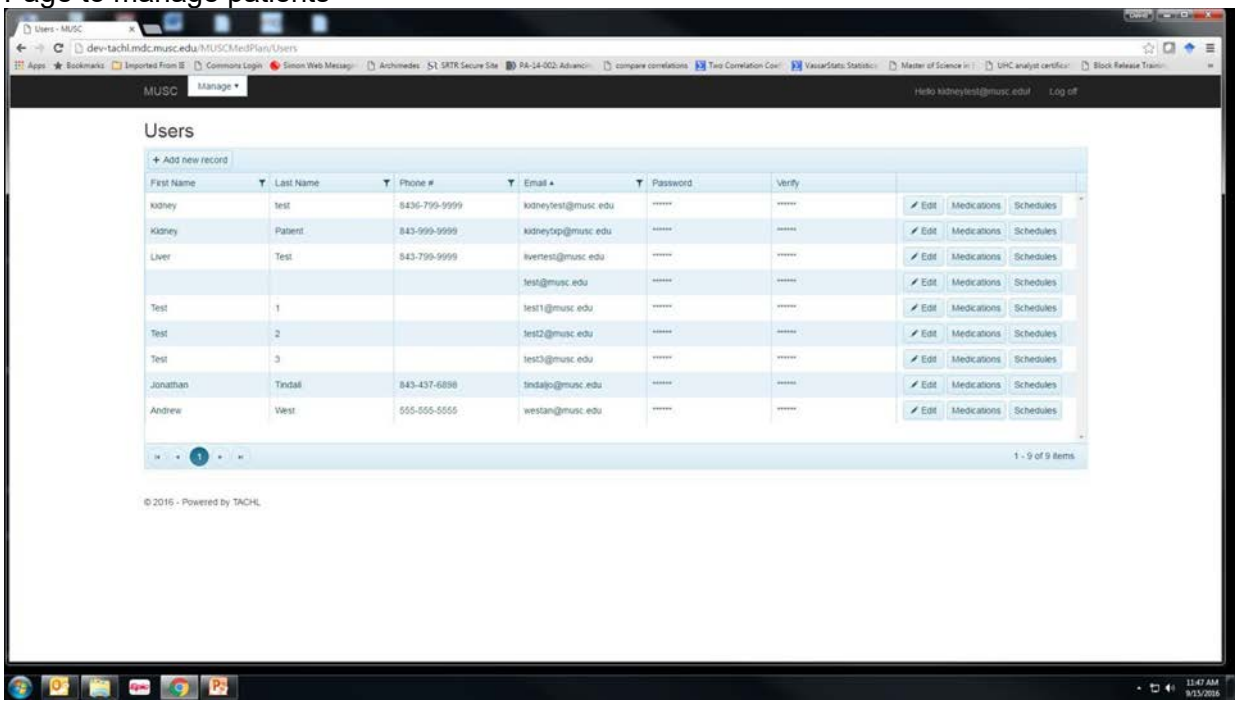
J Attachments

Screenshots of the mHealth app and web-based portal to manage medications and med adherence

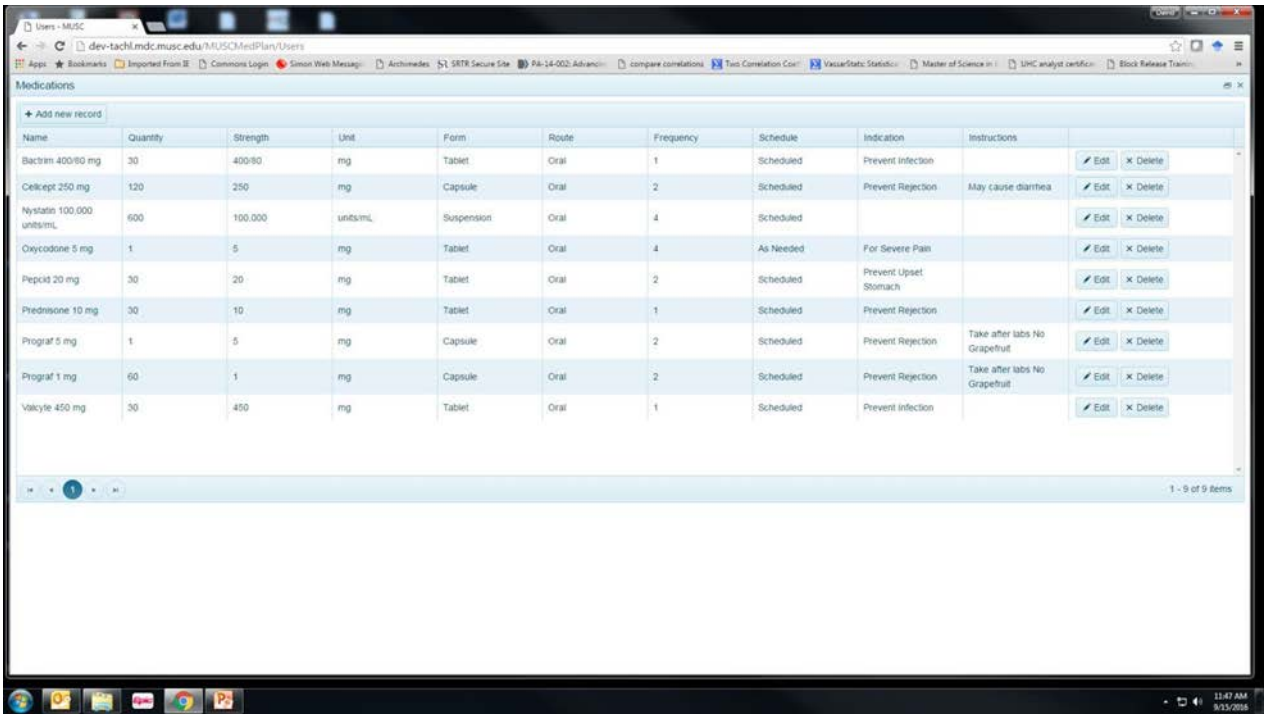
Welcome page to the web-based portal



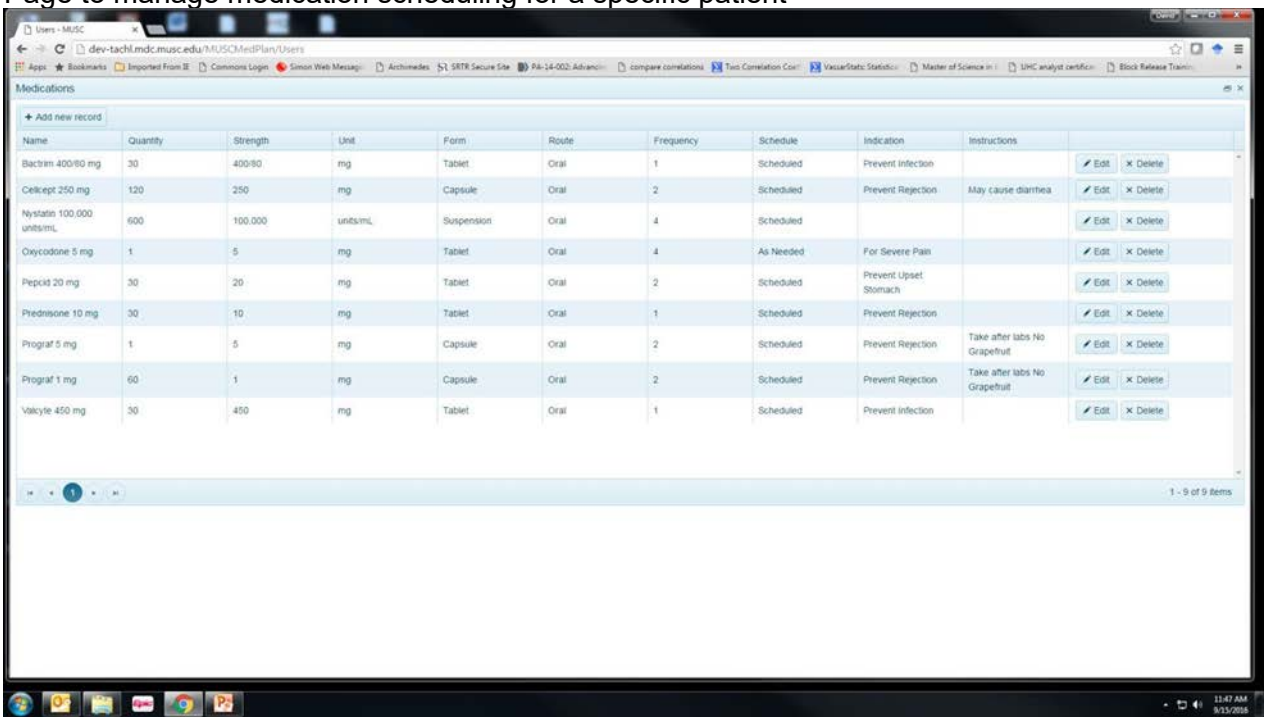
Page to manage patients



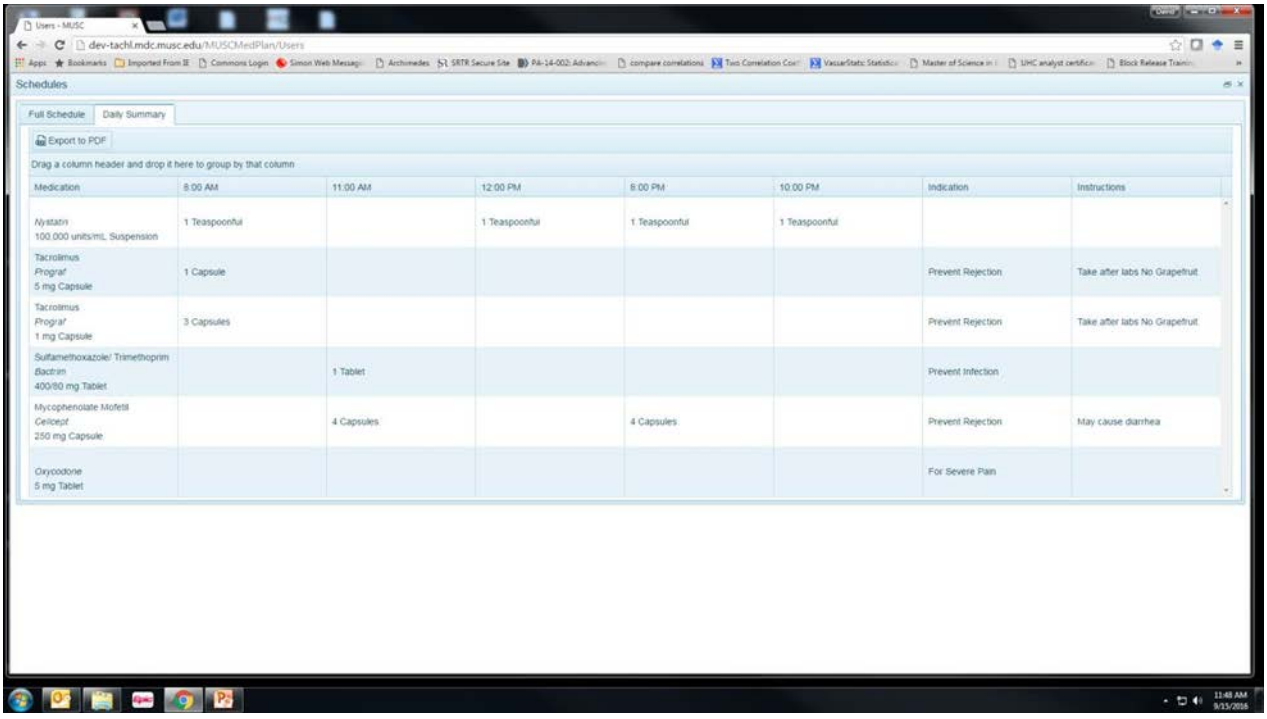
Page to manage medications for a specific patient



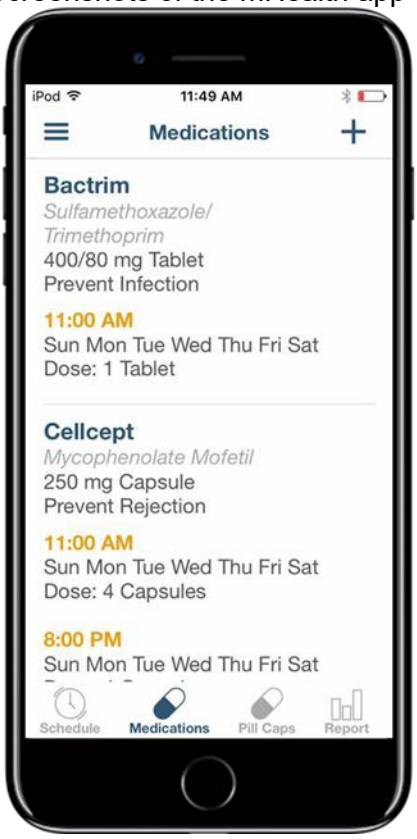
Page to manage medication scheduling for a specific patient

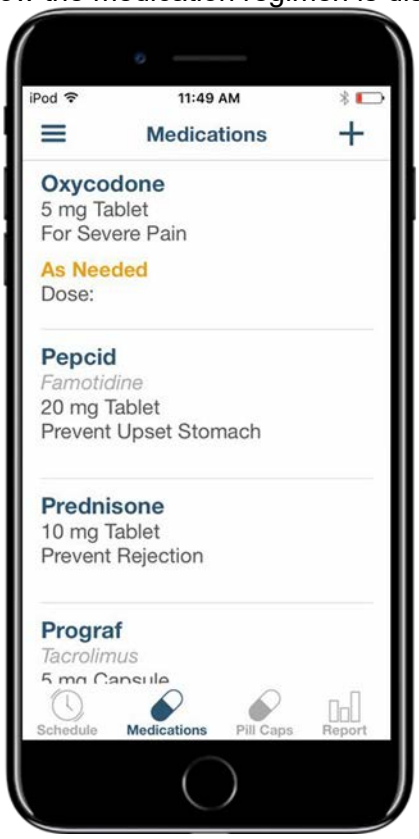


Display of regimen schedule for patient to view or to print off for a hardcopy

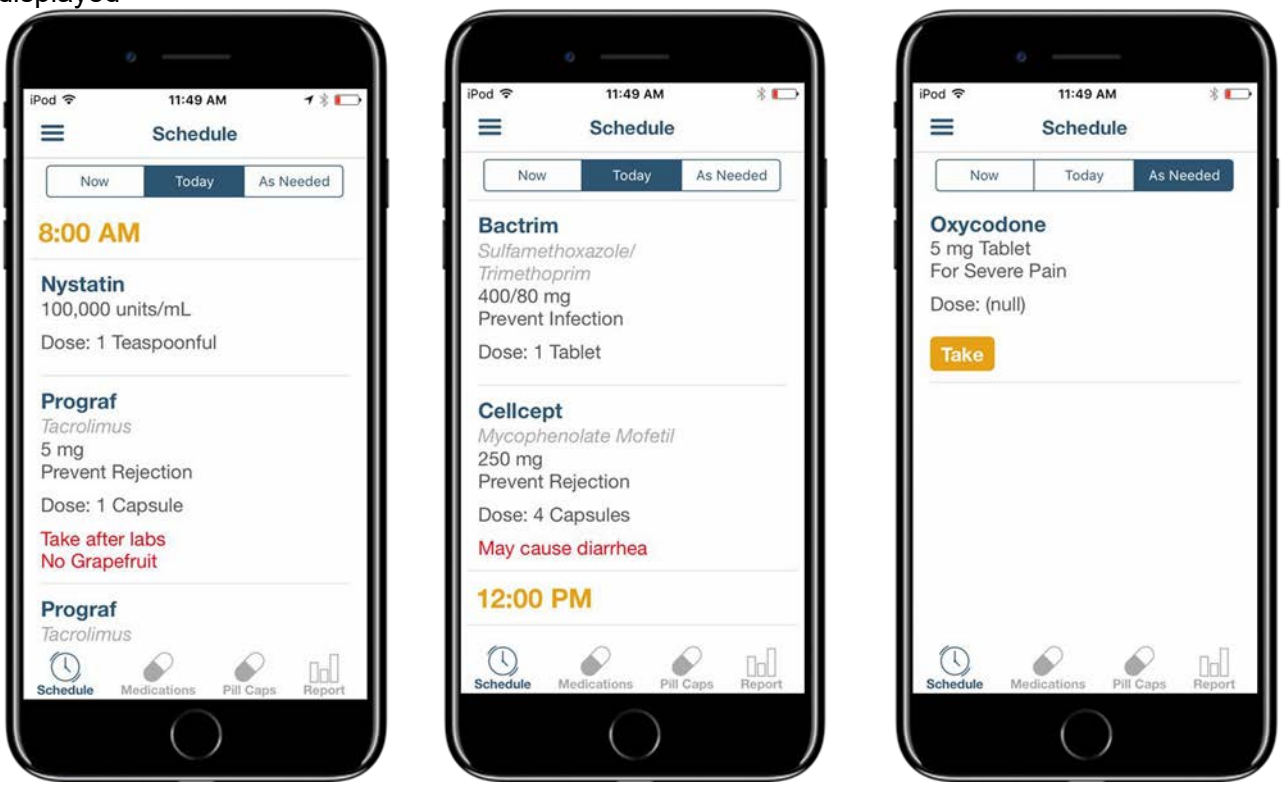


Screenshots of the mHealth app demonstrating how the medication regimen is displayed





Screenshots of the mHealth app demonstrating how the medication schedule is displayed



Screenshots of the mHealth app demonstrating how the medication adherence reporting function is displayed

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